Robert B. Sklaroff, M.D., F.A.C.P.
Medical Oncology/Hematology

Telephone: (215) 663-8200
Facsimile: (215) 663-8388
E-Fax: (215) 689-2461

Medical Arts Building - Suite #130
50 East Township Line Road
Elkins Park, PA 19027-2253

rsklaroff@comcast.net
http://www.doctor-bob.biz/rsklaroff

November 6, 2008

Spencer D. Ault, Esquire
The Law Office of Spencer D. Ault, Esquire
Stone Manor Associates
13193 Mountain Road
Lovettsville, VA 20180

re: Janelle Bailey Boroday Hill and Savannah Anne Hill

Dear Mr. Ault:

The records regarding the management of the above-named patient have been reviewed; the following conclusions have been drawn to a reasonable degree of medical probability.

This report is based on the information reviewed to-date, which I consider to be generally reliable—unless evidenced otherwise—and which are the type of data upon which I rely and are routinely relied upon by physicians and paraprofessionals when delivering care. If/when further data are acquired, the right is reserved to modify this report accordingly.

The opinions expressed herein are based on my education, training, and (28+ years') experience in assessing patients with conditions similar to those of this patient as has been depicted in the materials reviewed (including medical records, nursing records, laboratory reports, diagnostic tests and imaging, and consulting physician reports).

I graduated medical school at the Thomas Jefferson University (1974). I completed an Internal Medicine internship/residency program at the Henry Ford Hospital (1977); I then completed Hematology/Medical-Oncology Fellowships at the Memorial Sloan-Kettering Cancer Center (1979) and Hahnemann University (1980). I have been licensed in the Commonwealth of Pennsylvania (and have been in continuous practice) since 1979. Also, I am Board-Certified in Internal Medicine (1977) and Medical Oncology (1979); I am a Fellow of the American College of Physicians. I have had 27+ years' experience in practicing medicine in office settings, hospitals and others (*e.g.*, summer-camp doctor, private clinic, *locum tenens* for brief time-periods). I have worked with medical office and hospital staff, including medical technologists and nurses. Regarding assessment of the issues in this case, my specialty is similar to that of the involved practitioners.

I was a leader (at multiple levels) of Organized Medicine's Hospital (later "Organized") Medical Staff Section and was President of a Medical Staff. I am familiar with standards of the Joint Commission for the Accreditation of Healthcare Organizations.

I am familiar with (for my practice includes) medical conditions this patient experienced —as well as their complications and associated phenomena—that serve as the basis of this report. I am aware of the prevailing (and minimum) professional standards of care applicable to providing medical services (diagnostic/therapeutic, outpatient/inpatient) under like and similar circumstances as those encountered in this case, contemporaneous with when the patient was seen. I have participated in the development and use of protocols, policies and procedures for the care of patients with myriad medical conditions including those experienced by this patient. I can communicate how these conclusions apply to internists, medical oncologists and hematologists both nationally (for they do not differ greatly by community) and in the region of Loudoun County, Virginia.

The ethical approach to preparing this analysis adheres to the standards promulgated by a national professional society [American College of Obstetrics and Gynecology], to wit:

Expert Witness Affirmation

> As a member of the medical profession, I affirm my duty, when giving evidence or testifying as an expert witness, to do so solely in accordance with the merits of the case. I declare I will uphold these professional principles in providing expert evidence or expert witness testimony:
>
> I will always be truthful.
> I will conduct a thorough, fair and impartial review of the facts and the medical care provided, not excluding any relevant information.
> I will provide evidence or testify only in matters in which I have relevant clinical experience and knowledge in the areas of medicine which are the subject of the proceeding.
> I will evaluate the medical care provided in light of generally accepted standards, neither condemning performance that falls within generally accepted practice standards nor endorsing or condoning performance that falls below these standards.
> I will evaluate the medical care provided in light of the generally accepted standards which prevailed at the time of the occurrence.
> I will provide evidence or testimony that is complete, objective, scientifically based and helpful to a just resolution of the proceeding.
> I will make a clear distinction between a departure from accepted practice standards and an untoward outcome.
> I will make every effort to determine whether there is a causal relationship between the alleged substandard practice and the medical outcome.
> I will submit my testimony to peer review, if requested by a professional organization to which I belong.
> I will not accept compensation that is contingent upon the outcome of the litigation.

I have composed hundreds of reports, have been deposed on 60+ occasions, and have provided in-court testimony on 30+ occasions. I have never been disqualified as an expert witness, and none of my opinions has ever been disqualified in any administrative forum, court of law, or other legal proceeding. I have never been found guilty of fraud or perjury in any jurisdiction. I have no financial interest in the outcome of this case.

I have been advised that the definition of *Negligence* is as follows:

> *Negligence, when used with respect to the conduct of a physician means failure to use ordinary care, that is, failing to do that which a physician of ordinary prudence would have done under the same or similar circumstances or doing that which a physician of ordinary prudence would not have done under the same or similar circumstances.*

I have been advised the definition of *Proximate Cause* is as follows:

> *That cause which, in a natural and continuous sequence, produces an event, and without cause such event would not have occurred. In order to be a proximate cause, the act or omission complained of must be such that a health care provider, using ordinary care, would have foreseen that the event or some similar event might reasonably result therefrom. There may be more than one proximate cause of an event*.

The following Medical Records of Ms. Hill serve as the basis for this report:

Inovia Fairfax Hospital, Outpatient [1/8/2002 – 6/26/2002]
Inovia Fairfax Hospital, Inpatient [7/27/3003 – 8/12/2003]
Mubarik Ahmad Khan, M.D., Outpatient [3/9/2000 – 7/20/2004]
Homer Ellsworth Knudson, M.D., Outpatient [12/27/2001 – 6/9/2003]
Khurram Rashid, M.D., Outpatient [7/14/2003 – 7/21/2003]
Janelle Boroday Hill, Medical Bills [multiple dates]

The following Aventis Pharmaceuticals Filings also serve as the basis for this report:

Janelle Bailey Boroday Hill [7/15/2004 – 7/30/2004]
Adverse Event Reports [6/23/1993 – 11/5/2007]
Advertising Reports [6/9/2003 – 2/7/2008]

The following Medical Records of Savannah Anna Hill serve as the basis for this report:

Inovia Fairfax Hospital, Inpatient [7/27/2003 – 7/28/2003]
Inovia Fairfax Hospital, Inpatient [9/22/2003 – 9/23/2003]
Loudoun Hospital Center, Inpatient [7/27/2003 – 7/30/2003]
Catherine Raulerson, Ed.S., BCABA, Psychological Evaluation [12/7/2007]
Fairfax Identity, Paternity Evaluation [8/8/2003 – 8/12/2003]
St. Joseph's Hospital, Inpatient [7/24/2008 – 7/26/2008]

{two pages of information regarding the newborn's diagnoses have been deleted}

The following Depositions also serve as the basis for this report:

Mubarik Ahmad Khan, M.D. [4/22/2008]
Homer Ellsworth Knudson, M.D. [4/23/2008]
Khurran Rashid, M.D. [7/1/2008]
Vanessa E. Everhart [8/6/2008]
William David Hill [1/16/2007 & 1/17/2007]
Janelle Hill [12/18/2007 & 12/19/2007]
Julie Adkin Sites [3/5/2008]
Marcie K. Weil, M.D. [7/15/2008]
Michael Hill Willoughby, M.D. [8/18/2008]

Acute management of this patient deviated from acceptable professional standards; care, skill and/or knowledge exercised or exhibited in patient care by multiple physicians (and the institutions and entities which had definable oversight responsibilities for their actions and independent duties mutually exclusive of their specific professional work) was deficient. Specifically, due to the negligence of Khurram Rashid, M.D., the lack of oversight at Loudoun Hospital, and the deficient Lovenox (enoxaparin) labeling process by Aventis Pharmaceuticals, the patient's newborn suffered acute retinal hemorrhage. [The "patient" is Janelle Bailey Boroday Hill and her daughter is Savannah Anne Hill, a.k.a "Baby Boroday."] This report will not focus on managing fetal distress syndrome; rather, it will address the use of Lovenox in a pregnant woman and how it caused both the hemorrhage in the patient (which resolved) and the hemorrhage in the infant daughter (which caused *inter alia* ophthalmologic complications compounding neonatal damages).

Case Narrative

In ~1992, this 20 year-old woman [Birth Date: 7/29/1972] underwent 11-13 procedures to assess dysplasia, including a conization biopsy and cryosurgery. On 7/5/2001, she presented to Homer Ellsworth Knudson, M.D. for ongoing gynecologic management. Her past medical history was positive for minimal smoking (two packs annually) and drinking (one glass of wine monthly); she was allergic to various types of red dyes. She had undergone three abortions, had occasional depression and had noted headaches.

In May, 2001, she underwent a D & C for an incomplete abortion; on 7/5/2001, she was given an oral contraceptive but, on 12/27/2001, she reported she was using condoms. Pap smear revealed a "low-grade intraepithelial lesion" with "mild dysplasia and/or HPV/Condyloma." Thus, on 1/17/2002, culposcopy revealed a 50% shortened cervix with white scar tissue that precluded a complete evaluation. A cervical brush was inserted 1.5 cm. to perform a Pap smear and to do Human Papilloma Virus typing. [On 8/27/2002, repeat studies were negative for dysplasia and/or HPV.]

Meanwhile, on 3/9/2000, Mubarik Ahmad Khan, M.D. began providing primary care. On 4/27/2000, she was seen for cervical strain/sprain following a motor vehicle accident. On 5/25/2000, persistent pain prompted referral for physical therapy.

On 7/20/2000, persistent pain prompted referral to a neurosurgeon. On 10/19/2000, persistent pain prompted another referral. On 10/1/2001, symptoms had resolved. On 12/14/2001, she was given a Preventil Inhaler (prior to a trip to India).

On 7/29/2002, she experienced Deep Vein Thrombosis of the right poplitial vein documented by Doppler; it was noted to have improved on 8/15/2002. Work-up yielded normal determinations of the following potential causes of a hypercoagulable state: Factor V Leyden, Lupus Anticoagulant, Anti-Cardiolipin, Prothrombin Mutation, Proteins S/C, and Anti-Thrombin III. She continued taking Coumadin until 10/30/2002.

On 11/21/2002, she was noted to be pregnant (LMP 10/21/2002, EDC 7/24/2003). Thus, she was referred to see Homer Knudson, M.D. On 2/24/2003, she had another episode of DVT (right leg) which had resolved (as per a follow-up Doppler) by 3/3/2003. Lovenox was prescribed, and Dr. Khan planned for its continued use until 8/2003 (*i.e.*, so as to complete another half-year's therapy duration). On 5/30/2003, the patient expressed a desire to attenuate the dosage of her Lovenox; instead, the acquisition of a normal follow-up ultrasound on 7/3/2003 prompted her, on 7/7/2003, to have decreased her dose from 1 mg./kg. (every 12 hours) to 40 mg. (once daily); on that date, she expressed a desire to see a new obstetrician. On 7/21/2003, the pre-birth anticoagulation plan was established to entail stopping the Lovenox prior to induction. The next/final visits occurred on 12/8/2003 and 7/20/2004, following the hemorrhagic events depicted *infra*. [The rest of Dr. Khan's records demonstrate that the patient had a Pulmonary Embolism (as per an angiogram on 10/24/2003) in the right lower lobe; two other left lower lobe opacities suggested atelectasis had arisen from additional infarcts (from multiple PE's).]

Also, on 7/21/2003, Dr. Rashid decided to stop the Lovenox one day prior to induction.

The details of her obstetrical care, as noted previously, are deferred, although there was a chronology provided in the medical records that documented delay in addressing the development of fetal distress; this latter sequence-of-events had nothing to do with the use of Lovenox, although the safety of its use throughout the pregnancy is of-concern. In any event, the following is a time-line that detailed what transpired on 7/27/2003 following admission to Loudoun Hospital Center, as per the nurses' notes composed by Vanessa E. Everhart, R.N.C. (documenting late decelerations for 105 minutes):

12:35 tracing had been initiated without complication

12:41 patient complains of intense contractions

12:44 Dr. Rashid paged

13:00 possible late decelerations; patient repositioned to get better tracing

13:20 O2 MASK

13:30 patient repositioned, late decelerations persist, Dr. Rashid notified

> 13:48 late decelerations persist despite repositioning; MD aware and coming
>
> 14:01 patient more comfortable after Nuban, but late decelerations persist; MD aware
>
> 14:30 patient pushing call to Dr. Rashid; Dr. Willoughby in house
>
> 14:37 spontaneous rupture of membranes with thick green mecomium; neonatologist notified of need to attend delivery
>
> 14:39 Dr. Willoughby and neonatologist in room
>
> 14:45 delivered by spontaneous delivery a female infant with thick green meconium and clear sign that the baby had undergone fetal distress APGARS of 2, 9 at 1 and 5 minutes respectively

The following represents a commentary on the aforementioned events:

> Late decelerations are the type most indicative of fetal distress. One of the main reasons for doing fetal heart monitoring is to detect and to act upon this type of deceleration before a baby's condition becomes severely compromised; this is especially true when the late decelerations persist despite giving O2 and repositioning the patient.
>
> The nurse repeatedly documented that she had expressed explicit concern to Dr. Rashid about the late decelerations, but nothing was done. [Immediate emergency Caesarian Section should have been done within a few minutes of the detection of the fetal distress; it would have alleviated the problem, decreasing the risk of lifelong complications thereof.]
>
> Additionally, the patient had strong active labor documented for at least two hours before Dr. Willoughby arrived. The failure to act on the documented late decelerations is a failure to meet the minimum standard of care required in this case and this failure to meet the required minimum standard of care contributed to permanent damage that Savannah suffered due to her substandard birthing process. Parties at fault for this inaction may include Dr. Rashid, Dr. Willoughby, Loudoun Healthcare and the Loudoun County Hospital.

In a subsequently-filed form (with Aventis) entitled "MedWatch," Dr. Khan wrote that there had been a "possible" causal relationship between use of Lovenox (between the 3rd and 7th month of pregnancy) and subsequent development of the newborn's disabilities. This form (filed following an initial complaint issued on 7/15/2004) emphasized the fact that hemorrhage had transpired, rather than raising the possibility that circulating drug had been capable of causing a developmental anomaly (via trans-placental transfer).

Therefore, it is both necessary to assess the details of management @ Loudoun Hospital, and to review the relevant medical data regarding the potential for congenital anomalies.

In this regard, the following additional information has been gleaned from the chart. First, it was noted that the patient had had right eye surgery (on the admission form, composed @ 12:50 p.m. on 7/27/2003). At 12:44 P.M., it was noted that Dr. Rashid "plans to have as little intervention as possible and her doula is coming." Lovenox was restarted on 7/28/2003 (at 40 mg SQ daily) and she had no platelet autoantibodies. Following provision of narcotics for prn-pain, she was discharged on 7/30/2003. Finally, noted is a negative venous Doppler, acquired upon admission (probably as a baseline). [The newborn's history-form noted that her father and brother had lactose intolerance.]

The placenta showed significant infarction and umbilical venous thrombosis; these were ascribable either to maternal hypertension or to systemic lupus erythematosis. Here, the underlying anomaly was maternal-uteroplacental vascular insufficiency, whereas the "minor degree of acute chorioamnionitis" was felt to be a mutually exclusive finding. [The results of any placental toxicology were not included in this version of the chart.]

Rather than recapitulating events that occurred following birth, the Discharge Summaries have been reproduced herein; the baby was transferred on 7/28/2003 to Fairfax Hospital. Also included is the Intrauterine Growth Graph; it depicts the fact that this term-baby had a length of only 47 cm. (5%'ile), a weight of only 2774 gm. (~20%'ile) and a head circumference of 345 cm. (50%'ile). These anomalies could not have transpired in any acute time-frame associated with hemorrhagic complications of childbirth; they must have occurred while the patient's pregnancy was transpiring, resulting in the multiple developmental deficiencies (associated with *inter alia* intraventricular hemorrhage). Mother/child had blood-type "O+/O-" and, thus, there was no hydrops fetalis.

It is impossible to define "two points on the curve" during the newborn's hospitalization; thus, it must be concluded that treatment of hemorrhage (with platelets and Vitamin K) did not yield additional harm to the patient. Whether the facilities at this institution were sufficient to handle the acute medical needs herein is a query deferred to a neonatologist. The same is true for additional findings of significant import, such as hypoxia (41.8%). Ultimately, the placental pathology and the newborn's anomalies must be correlated although, again, determining this effort's impact principally rests with other consultants.

Profound elevation of PT (>60) was accompanied by profound thrombocytopenia (35K) …but a normal aPTT (23); this suggests that a DIC (Diffuse Intravascular Coagulation) process had been initiated by the overdose of Lovenox (and that platelets were consumed in an effort to control hemorrhage), but that a generalized paradoxical syndrome of a bleeding/clotting combination was not a predominant sequella (noting the reactive elevation of Fibrinogen to 1000+, although the other far more specific DIC-activity parameter—Fibrin Split Products/ Monomer—was neither drawn nor followed seriatim). Finally, noting the normal Hemoglobin, the positive cord-blood Coombs was irrelevant, both diagnostically and therapeutically); leukocytosis was reactive and not unexpected. Thus, the impact of the recently-discontinued Lovenox had both acute/chronic factors.

{double Discharge Summaries and a Growth-Curve have been deleted}

Six distinct components exist regarding the medical malpractice issue. As noted *supra*, assessment of obstetrical care by Drs. Rashid and Willoughby following admission to the Loudon Hospital Center is deferred, although it must be emphasized that standards used by the Joint Commission for the Accreditation of Healthcare Organizations (JCAHO) include the necessity to assess the roles of paraprofessionals and administrative personnel (roles played by nurses, for example, if they encounter a problem that they feel has not been adequately assessed by a physician and fail to report this concern promptly). Thus, failure to act after detection of late decelerations would impugn the nurses and hospital. As a corollary, this physician is obviously unable to assess ophthalmologic management.

On the other hand, therefore, this physician must focus upon the factors that affected the decision to prescribe Lovenox, not withstanding whatever dosage was being employed. This encompasses both the practitioners (Drs. Khan and Rashid) and the manufacturer (Aventis Pharmaceuticals), taking into account the manufacturer's Lovenox-database.

The Fairfax records are notable for a few key reasons, cited to focus pivotal concerns. First, the Discharge Physical Examination confirmed the poor intrauterine development (citing almost identical %'ile determinations). Second, the issue of whether the patient had been exposed to Cocaine was raised, per a communication that occurred on 8/4/2003. Although a verbal report regarding the placenta was received, it couldn't be verified. Perhaps there was an issue related to chain-of-custody but, for whatever reason, this is an entry that was specifically crossed-off of the "Hospital Course Cumulative Data." Therefore, also noting that the patient had denied such exposure, it will be assessed (because of the need for due diligence), but it is considered initially to be a non-factor.

In any case, the Face Sheet stated that the Primary Diagnosis was "Intraventricular hemorrhage of newborn, grade II," and that the Secondary Diagnoses included:

> Convulsions in newborn
> Transient neonatal thrombocytopenia (7days)
> Hemolytic disease of newborn due to unspecified isoimmunization
> Hypocalcemia and hypomagnesimia of newborn
> Cerebral thombosis with cerebral infarction (7 days)
> Hyperkalemia
> Other form of retinal detachment (says error; 15 days)
> Cocaine affecting newborn via placenta/breast milk (says error; 9 days)
> Unspecified hearing loss
> Stridor
> Vitreous hemorrhage
>
> Meconium positive for cocaine (according to lab call on 8/4/03; urine screen negative for cocaine) ("unable to confirm" as per records, page 33) (no contemporaneous progress note as per records, pages 109-110)

The admission hematology consultation has also been reproduced in its entirety, reflecting the initial confusion as to what had been the cause of severe thrombocytopenia.

{14 pages have been deleted; this comprise a summary of the infant's diagnoses, the hematology consultation, and multiple "special coagulation" laboratory reports}

These hematologic data are not confirmatory of any congenital coagulopathy; anomalies may be ascribed to the fact that the patient had received blood products and was not tested in a baseline fashion (as had been the case prior to transfer from Loudoun). Also, there was no testing for Heparin-induced activator antibodies (to assess for HIT), an idea that had been raised in the follow-up (dictated/typed) Hematology consultation.

A summary of follow-up evaluations illustrates the lifelong disabilities being suffered; again, just as is the case with other subspecialty input, these raw data are merely being recounted to confirm the sequellae ascribed totally to events transpiring at birth:

> Medical Evaluation at San Diego Regional Center [page 4 of outpatient services records] shows the brain and eye hemorrhages were felt to have been secondary to fetal exposure to the maternal anticoagulant.
>
> Savannah underwent removal of a blood clot with from the vitreous of her right eye in 9/2003 at about 8 weeks of age with subsequent total retinal detachment of that eye [Page 62 of Fairfax Hospital records, 8/3/2003].
>
> Since 10/2003, she has lost all detectable vision from her right eye and any further surgery is unlikely to restore any useable vision, according to Dr. Richard Birdsong, a pediatric ophthalmologist [page 6].
>
> 16 month-old girl with mild to moderate delayed development in gross motor and language areas, according to Dr. Joan Reece, Diplomat in neuro-developmental disabilities [page 9].
>
> History of enoxaparin exposure *in utero*, in second and third trimesters, birth trauma, with intraventricular bleeds, of white mater, grey mater and retinas, thrombocytopenia, sensineural hearing loss, blindness in the right eye with 20/100 in the left eye. Impression moderately severe speech and language impairment due to senisorineural hearing loss [page 13].
>
> On 11/11/2004, Occupational therapy pediatric evaluation yielded developmental delay, thrombocytopenia, birth defects from Lovenox [page 19].
>
> On 11/8/2004, a Developmental questionnaire noted she had been born with passive bleeds white matter, grey matter, retinal, etc., has permanent hearing and vision impairments. The blindness in the right eye was caused by an eye surgery. Otherwise her birth related injuries pertain to an enoxaparin exposure [page 22].
>
> On 2/4/2004, the EEG was normal [page 95].

{Allusion is made in the second deposition of the patient [page 279:line 9] to her having produced answers to interrogatories; these have not been provided for review but it is assumed no major additional information is contained therein, on a medical plane.}

In the first deposition, she established herself as a gainfully-employed, quite-responsible woman and, even when hospitalized in Reston for psychiatric reasons, her recollection was primarily related to her need to detox from codeine-type drugs (and whatever else she had found in the medicine cabinet that had been placed therein by her husband).

Thus, there was no support for her use of cocaine and, indeed, she expressed ongoing concern regarding the well-being of the fetus episodically in her unguarded comments. She had become "medication averse" [40:20] and, thus, there is no historical support for a presumptive diagnosis that she had abused cocaine during the index-pregnancy. Indeed, she had used Ambien but, otherwise, she even rejected treatment for constipation [42:21].

She described her rationale for having filed suit [63:12 *et seq.*], the fact that the Doula organization was intended to provide support for military wives [73:5] and that its use could decrease overall analgesic needs [77:17], and her overall mien/status [throughout]. Also, she explained that she switched obstetricians due to her husband's input [89:20].

During the bulk of the deposition(s), she discussed her personal life but, near the end, she elaborated more on the use of anticoagulants during her pregnancy. She said that Dr. Khan told her that her choice was between using Heparin and Lovenox [472:5], noting that Coumadin was not an option [472:10]. Thereafter, she used Aspirin [476:6]. She had a negative family history of clotting disorders [475:9]. She noted that the use of Lovenox caused easy bruisability [484:1], but she said Dr. Khan did not discuss acquiring monitoring tests (such as activated-X) to assess the efficacy of this agent [488:17].

There was episodic discussion as to when she took her last Lovenox injection (pre-birth); she had noted contractions (2 minutes apart) on Thursday (prior to going to see a movie). After she said that she had taken shots on Thursday and, possibly, on Friday-a.m., discussion of this issue appeared to conclude following this exchange [page 521]:

Q. If the records reflect that you had ceased taking the Lovenox three days before your going to Loudoun Hospital, would you have any reason to disagree with that?

A. Well, that would fall in the parameter of me not taking it Thursday because it would have been Friday, Saturday, Sunday.

Q. That's my point.

A. Sure. That sounds reasonable.

She also said that she did not recall if anyone at the Loudoun Hospital Center inquired as to when she had taken her most recent anticoagulant shot [521:1]. Otherwise, the rest of the deposition related to litigation-related processes (such as the MedAlert Report filing) and to the current status of her daughter (attending a Special Needs school, full-time).

The patient's husband confirmed the essentials of the history in his two-part deposition, including the fact that the last Lovenox dosage had been given around the time they had gone to the movies on Thursday [108:22], the day contractions had first been noted.

Marcie Weil, M.D. discussed events that occurred post-transfer; the hematologic values worsened before they improved. She otherwise had no new diagnostic opinion [65:16].

Vanessa Everhart, R.N. noted the Lovenox had last been given on 7/24/2003 [77:9]. She confirmed the fact that there had been early decelerations (of the pulse) [102:1], and that this type of information would be conveyed routinely to the physician [102:9].

Michael Hill Willoughby, M.D. confirmed the accuracy of his one progress note [9/3].

Julie Adkin Sites, the doula, did not see Dr. Rashid in the room during labor [136:10].

Homer Ellsworth Knudson, M.D. stated he would not manage anticoagulants [43:8].

Khurran Rashid, M.D. said he and Dr. Khan agreed that it would be wise to discontinue use of Lovenox 24-hours prior to induction at 38-weeks gestation [72:3]. Surprisingly, he did not immediately go to the hospital after having learned the patient was having potential complications of labor that could indicate fetal distress on monitoring [168:17]. Also, he has never discussed this delivery with Dr. Willoughby [178:20], despite the fact that this physician was covering for him, presumably until he was to arrive urgently. {The rest of the discussion of the delivery process is deferred to that subspecialist.}

Mubarik Ahmad Khan, M.D. said that the possibility was raised that the placenta was crossed by autoantibodies to platelets, which then adversely affected the fetus [72:16]. Otherwise, he repeatedly noted that other resources supported his use of Lovenox. Also, he noted that this medication is not routinely monitored by lab tests [112:19 & 131:5]. And he reduced the dosage due to bleeding/itching [279:21], raising the prospect that the capacity existed for subclinical bleeding to occur on what was viewed as a standard dose. He saw no reason to acquire an anti-Factor Xatest [282:21]. Throughout, he relied upon the Aventis packaging that stated it was not unsafe to use this agent during pregnancy.

To summarize, prior to recapitulating both the specific/general medical literature herein, this patient had two facets to her management which are under scrutiny in this litigation. First, her obstetrical management is viewed as sub-optimal, for she was demonstrating fetal distress for an extended period during labor before she actually delivered her child. Second, her use of Lovenox is viewed as problematic, for the newborn suffered severe neurological damage from intracerebral bleeding associated with an acute coagulopathy. That the baby was small-for-age is also of-interest, and that the patient's placenta was pathologically abnormal provides a clue as to the pathogenesis of what transpired. Although it is viewed as a lab-error, the positive cocaine-screen must also be addressed. Essentially, the obstetricians defer to the judgment of Dr. Khan, who invokes Aventis. These two processes appear mutually exclusive for, even if the bleeding was starting earlier than on 7/27/2003, its profound manifestations were not yet being appreciated.

This is the pertinent information provided by Aventis regarding Lovenox use [with data related thereto cited herein *supra*, starting on page 73]:

> Treatment of Deep Vein Thrombosis With or Without Pulmonary Embolism: In outpatient treatment, patients with acute deep vein thrombosis without pulmonary embolism who can be treated at home, the recommended dose of Lovenox Injection is 1 mg/kg every 12 hours administered SC. In inpatient (hospital) treatment, patients with acute deep vein thrombosis with pulmonary embolism or patients with acute deep vein thrombosis without pulmonary embolism (who are not candidates for outpatient treatment), the recommended dose of Lovenox Injection is 1 mg/kg every 12 hours administered SC or 1.5 mg/kg once a day administered SC at the same time every day. In both outpatient and inpatient (hospital) treatments, warfarin sodium therapy should be initiated when appropriate (usually within 72 hours of Lovenox Injection). Lovenox Injection should be continued for a minimum of 5 days and until a therapeutic oral anticoagulant effect has been achieved (International Normalization Ratio 2.0 to 3.0). The average duration of administration is 7 days; up to 17 days of Lovenox Injection administration has been well tolerated in controlled clinical trials.
>
> Laboratory Tests: Periodic complete blood counts, including platelet count, and stool occult blood tests are recommended during the course of treatment with Lovenox Injection. When administered at recommended prophylaxis doses, routine coagulation tests such as Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT) are relatively insensitive measures of Lovenox Injection activity and, therefore, unsuitable for monitoring. Anti-Factor Xa may be used to monitor the anticoagulant effect of Lovenox Injection in patients with significant renal impairment. If during Lovenox Injection therapy abnormal coagulation parameters or bleeding should occur, anti-Factor Xa levels may be used to monitor the anticoagulant effects of Lovenox Injection.
>
> Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term studies in animals have been performed to evaluate the carcinogenic potential of enoxaparin. Enoxaparin was not mutagenic in in vitro tests, including the Ames test, mouse lymphoma cell forward mutation test, and human lymphocyte chromosomal aberration test, and the in vivo rat bone marrow chromosomal aberration test. Enoxaparin was found to have no effect on fertility or reproductive performance of male and female rats at SC doses up to 20 mg/kg/day or 141 mg/m 2 /day. The maximum human dose in clinical trials was 2.0 mg/kg/day or 78 mg/m^2 /day (for an average body weight of 70 kg, height of 170 cm, and body surface area of 1.8 m^2).

Pregnancy: Pregnancy Category B:
All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure. The fetal risk summary below describes Lovenox's potential to increase the risk of developmental abnormalities above background risk.

Fetal Risk Summary:
Lovenox is not predicted to increase the risk of developmental abnormalities. Lovenox does not cross the placenta, based on human and animal studies, and shows no evidence of teratogenic effects or fetotoxicity.

Clinical Considerations:
It is not known if dose adjustment or monitoring of anti-Xa activity of enoxaparin are necessary during pregnancy.

Pregnancy alone confers an increased risk for thromboembolism that is even higher for women with thromboembolic disease and certain high risk pregnancy conditions. While not adequately studied, pregnant women with mechanical prosthetic heart valves may be at even higher risk for thrombosis. Pregnant women with thromboembolic disease, including those with mechanical prosthetic heart valves, and those with inherited or acquired thrombophilias, also have an increased risk of other maternal complications and fetal loss regardless of the type of anticoagulant used.

All patients receiving anticoagulants such as enoxaparin, including pregnant women, are at risk for bleeding. Pregnant women receiving enoxaparin should be carefully monitored for evidence of bleeding or excessive anticoagulation. Consideration for use of a shorter acting anticoagulant should be specifically addressed as delivery approaches (see BOXED WARNING, SPINAL/EPIDURAL HEMATOMAS).

Hemorrhage can occur at any site and may lead to death of mother and/or fetus. Pregnant women should be apprised of the potential hazard to the fetus and the mother if enoxaparin is administered during pregnancy.

Data

Human Data - There are no adequate and well-controlled studies in pregnant women.

A retrospective study reviewed the records of 604 women who used enoxaparin during pregnancy. A total of 624 pregnancies resulted in 693 live births. There were 72 hemorrhagic events (11 serious) in 63 women. There were 14 cases of neonatal hemorrhage. Major congenital anomalies in live births occurred at rates (2.5%) similar to background rates.

> There have been post marketing reports of fetal death when pregnant women received Lovenox Injection. Causality for these cases has not been determined. Insufficient data, the underlying disease, and the possibility of inadequate anticoagulation complicate the evaluation of these cases.
>
> Animal Data - Teratology studies have been conducted in pregnant rats and rabbits at SC doses of enoxaparin up to 30 mg/kg/day or 211 mg/m 2 /day and 410 mg/m 2 /day, respectively. There was no evidence of teratogenic effects or fetotoxicity due to enoxaparin. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
>
> Cases of "Gasping Syndrome" have occurred in premature infants when large amounts of benzyl alcohol have been administered (99-405 mg/kg/day). The multiple-dose vial of Lovenox solution contains 15 mg/1.0 mL benzyl alcohol as a preservative (see WARNINGS, Miscellaneous).
>
> Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Lovenox Injection is administered to nursing women

Six distinct components exist regarding the medical malpractice issue [per page 16]. First, the obstetrical care by Drs. Rashid and Willoughby through Loudoun (and nursing, Ms. Everhart) is to be critiqued by another subspecialist; apparently, the latter physician was invoked at the last minute (almost literally) and, thus, at-issue is lack of availability of the former physician. Therefore, the focus is trained on Dr. Rashid and Loudon. Second, the initial decision to initiate Lovenox was made by Dr. Khan, whose conduct was informed by the information disseminated by Aventis. Therefore, the focus is trained on Aventis. Third, the initial obstetrical care by Dr. Knudson accommodated this anticoagulation decision (understandably) without critique and Dr. Weil's input did not commit her to ongoing management decisions. It is for this set of reasons that the distillation of the database yields focus on Drs. Rashid and Loudon (for final care) and on Aventis (for prodromal events). As introduced earlier [per page 6], the patient suffered intracerebral bleeding (including retinal hemorrhage) as a result, with lifelong import.

The issue of cocaine-use must be confronted, and put to rest. The pathologist's report (regarding the placenta) was never confirmed, and litigation has been filed that is based on "defamation of character" and "violation of policy" with regard to this document. Also, it is noted that subsequent toxicology of the baby was negative, and Dr. Khan had not documented any evidence that she was a drug-user. Thus, because such issues as "chain of custody" are beyond the realm of this report (and other subsequently-acquired data apparently document the absence of drug-use by the patient, per information/belief), it is not suspected that she was a drug-user. Nevertheless, an Internet-based analysis is provided herein to demonstrate that the hemorrhagic findings could not be from cocaine. This is also provided to counterpoint what is felt to have been the pathophysiology.

Thus, this citation has been provided, as per the American Pregnancy Association:

> **How can cocaine affect my unborn baby?** According to the Organization of Teratology Information Services (OTIS), during the early months of pregnancy, cocaine exposure may increase the risk of miscarriage. Later in pregnancy, cocaine use can cause placental abruption. Placental abruption can lead to severe bleeding, preterm birth, and fetal death. OTIS also states that the risk of a birth defect appears to be greater when the mother has used cocaine frequently during pregnancy. According to the American College of Obstetricians and Gynecology (ACOG), women who use cocaine during their pregnancy have a 25 % increased chance of premature labor. Babies born to mothers who use cocaine throughout their pregnancy may also have a smaller head and have their growth hindered. Babies who are exposed to cocaine later in pregnancy may be born dependent and suffer from withdrawal symptoms such as tremors, sleeplessness, muscle spasms, and feeding difficulties. Some experts believe that learning difficulties may result as the child gets older. Defects of the genitals, kidneys, and brain are also possible.
>
> http://www.americanpregnancy.org/pregnancyhealth/illegaldrugs.html

Cocaine exposure increases the risks of miscarriage, *abruptio placentae*, premature birth, birth defects, smaller heads, and growth hindrance, addiction, learning difficulties, and defects (of the genitals, kidneys and brain). This patient had none of these complications, for the primary event was hemorrhagic (recalling the coagulopathy, *vide supra et infra*). Specifically, all either did not occur or were secondary to the intracerebral hemorrhage.

In an effort to clarify the direction of this analysis (and then to demonstrate how these data culminate in a set of conclusions that is consistent therewith and remains durable), the underlying neurological diagnosis of Baby-Savannah is now to be articulated. It is recognized that subsequent evaluations/treatments for Non-Epileptic Paroxysmal Events, Developmental Delay and Cerebral Palsy are viewed as being secondary to an underlying diagnosis of Periventricular Leukomalacia {"PVL"} from the neonatal hemorrhage:

Periventricular Leukomalacia

> *Background*
>
> Periventricular leukomalacia (PVL) is the most common ischemic brain injury in premature infants. The ischemia occurs in the border zone at the end of arterial vascular distributions. The ischemia of PVL occurs in the white matter adjacent to the lateral ventricles. The diagnostic hallmarks of PVL are periventricular echodensities or cysts detected by cranial ultrasonography. Diagnosing PVL is important because a significant percentage of surviving premature infants with PVL develop cerebral palsy (CP), intellectual impairment, or visual disturbances.

Pathophysiology

The pathophysiology of PVL is a complex process. PVL may occur because of ischemia-reperfusion injury to the periventricular area of the developing brain or because of cytokine-induced damage following maternal or fetal infection.

PVL is a white matter lesion in premature infants that may result from hypotension, ischemia, and coagulation necrosis at the border or watershed zones of deep penetrating arteries of the middle cerebral artery. Decreased blood flow affects the white matter at the superolateral borders of the lateral ventricles. The site of injury affects the descending corticospinal tracts, visual radiations, and acoustic radiations.

In addition to possible ischemic injury, PVL may be the result of edema fluid and hemorrhage that cause compression of arterioles in the white matter. Reperfusion injury by free radicals to developing oligodendrocytes in the fetal or premature infant's brain may play an important role in the pathogenesis of PVL.

Premature infants have impaired cerebrovascular blood flow autoregulation and are susceptible to intracranial hemorrhage (ICH) as well as PVL. Premature infants on mechanical ventilation may develop hypocarbia. Several studies have linked hypocarbia, particularly in the first few days of life, with the development of PVL.

The relationship of maternal infection, placental inflammation, and vasculitis to the pathogenesis of PVL remains controversial. Some investigators have demonstrated an association of chorioamnionitis and cytokines with PVL although others have not.

Following the initial insult, whether ischemia-mediated or cytokine-mediated, white matter damage occurs. The white matter damage likely occurs because of selective loss of oligodendrocytes.

http://www.emedicine.com/ped/topic1773.htm

It is appropriate at this juncture to distill key-conclusions that have emerged from the case-review summarized *supra*. First, the low birth-parameters illustrate that an adverse event occurred *in utero*. Second, the existence of intra-cerebral hemorrhage illustrates that the adverse event was hematologic. Third, the facts that the patient herself did not hemorrhage and that the drug's duration-of-action is dissipated when it has been stopped as much as three days prior to an event illustrate that the patient was not anticoagulated at the time when the baby was born. Fourth, the fact that the patient's fetal monitoring was apparently sub-par illustrates that the effects of fetal hemorrhage (not maldevelopment) were exacerbated by hypoxia suffered prior to the time when delivery actually occurred.

If problems with the use of Lovenox existed in this patient with a high-risk pregnancy, alternative drugs must have been available contemporaneously; to establish this fact, therefore, a listing thereof (establishing each class/subclass available) may be invoked:

Vitamin K antagonists	Acenocoumarol • Clorindione • Coumatetralyl • Dicoumarol (Dicumarol) • Diphenadione • Ethyl biscoumacetate • Phenprocoumon • Phenindione • Tioclomarol • Warfarin
Heparin group	Antithrombin III • Danaparoid • Heparin • Sulodexide • *low molecular weight heparin* (Bemiparin, Dalteparin, Enoxaparin, Nadroparin, Parnaparin, Reviparin, Tinzaparin)
Glycoprotein IIb/IIIa inhibitors	Abciximab • Eptifibatide • Tirofiban
Other platelet aggregation inhibitors	Acetylsalicylic acid/Aspirin • Aloxiprin • Ditazole • Carbasalate calcium • Cloricromen • Dipyridamole • Indobufen • Picotamide • Triflusal • *ADP receptor inhibitors* (Clopidogrel, Ticlopidine, Prasugrel) • *prostaglandin analogue* (Beraprost, Prostacyclin, Iloprost, Treprostinil)
Enzymes	*plasminogen activators* (Alteplase/Reteplase/Tenecteplase, Streptokinase, Urokinase/Saruplase, Anistreplase) • *other serine endopeptidases* (Ancrod, Drotrecogin alfa/Protein C, Fibrinolysin) • Brinase
Direct thrombin inhibitors	Argatroban • Bivalirudin • Dabigatran • Desirudin • Hirudin

	• Lepirudin • Melagatran • Ximelagatran
Other antithrombotics	Apixaban • Defibrotide • Dermatan sulfate • Fondaparinux • Idraparinux • Otamixaban • Rivaroxaban
Non-medicinal	Citrate • EDTA • Oxalate

[http://en.wikipedia.org/wiki/Category:Anticoagulants]

Certain of these agents would also not be indicated in pregnant patients, but the following article illustrates what could have been considered:

Management of heparin-associated thrombocytopenia in pregnancy with subcutaneous r-hirudin

Auteur(s) / Author(s)

HUHLE G. (1) ; GEBERTH M. (2) ; HOFFMANN U. (1) ; HEENE D. L. (1) ; HARENBERG J. (1) ;

Affiliation(s) du ou des auteurs / Author(s) Affiliation(s)

(1) 1st Department of Medicine, Faculty of Clinical Medicine Mannheim, ALLEMAGNE

(2) Department of Obstetrics and Gynecology of the University of Heidelberg, ALLEMAGNE

Résumé / Abstract

Heparin-induced thrombocytopenia type II is a serious, immune-mediated complication of heparin therapy. Due to its low cross-reactivity with heparin-associated antibodies (10-20%), danaparoid has successfully been administered in these patients. In recent studies, r-hirudin as a potent and specific thrombin inhibitor, was demonstrated to be a safe and effective anticoagulant. We report a pregnant woman with systemic lupus erythematosus and recurrent venous thromboembolism who suffered from heparin-induced thrombocytopenia type II while treated with dalteparin sodium. Positive cross-reactivities with danaparoid were found. Anticoagulation with 15 mg subcutaneous r-hirudin was performed twice daily from the 25th week of pregnancy until delivery. No thromboembolism or bleeding or fetal toxicity of r-hirudin was detected. ***Recombinant hirudin is a potent and specific thrombin inhibitor that can be used as a safe and effective anticoagulant in pregnancy.***

Revue / Journal Title

Gynecologic and obstetric investigation **ISSN** 0378-7346 **CODEN** GOBIDS

Source / Source

2000, vol. 49, n°1, pp. 67-69 (5 ref.)

[http://cat.inist.fr/?aModele=afficheN&cpsidt=1256223]

Therefore, the theory-of-this-case is that Lovenox crossed the placenta, as illustrated by its pathology (old/new clots) that shows multiple prior hemorrhagic events had occurred. The pathogenesis of this process (*e.g.*, Heparin-Induced Thrombocytopenia, "HIT") must be established, along with whether Aventis should have known that this eventuality could occur in a high-risk pregnancy patient using Lovenox on a long-term basis. Indeed, whether use of a monitoring test should have been advised by Aventis is also at-issue. Overall, the distilled-question is whether Aventis knew or should have known that the published warnings did not encompass established complication-risks and, therefore, have ensured that the Food and Drug Administration had been apprised of these issues (thereby ensuring that the medical community and the patient population had been properly educated regarding the "informed consent" process that was necessary).

One frame of reference that is to be employed is whether the accumulated data regarding hematologic toxicity met or exceeded that which had prompted Aventis to have issued a boxed-warning regarding a risk of spinal hematoma (following 19 case-reports). Again, correlative is whether such data should have prompted Aventis to have recommended use of a monitoring test (or, at the very least, have studied the potential for this approach).

Regarding the monitoring issue, it has been noted that the medical literature includes studies of Anti-Xa, Enox and ACT testing. Even if such studies might have had limited availability, safe use of Lovenox would have necessitated issuance of ways to acquire such data (by sending the patient to a tertiary center or the blood to a reference lab). Further, the following article serves as an example of the key-literature in this regard:

http://content.onlinejacc.org/cgi/content/full/41/3/394

The activated clotting time can be used to monitor the low molecular weight heparin dalteparin after intravenous administration

Jonathan D. Marmur, MD, FACC[*,*], Sunil X. Anand, BA[†], Ramanjit S. Bagga, MD[†], Jawed Fareed, PhD[‡], Chi-Miau Pan, PhD[§], Samin K. Sharma, MD, FACC[†] and Merwin F. Richard, MD[†]

[*] Department of Medicine, Division of Cardiology, SUNY Health Science Center at Brooklyn, Brooklyn, New York, USA
[†]Zena and Michael A. Weiner Cardiovascular Institute, Mount Sinai School of Medicine, New York, New York, USA
[‡]Hemostasis and Thrombosis Research Laboratories, Loyola University Medical Center, Maywood, Illinois, USA
[§]Research Division, International Technidyne Corporation, Edison, New Jersey, USA

Manuscript received April 3, 2002; revised manuscript received August 5, 2002, accepted August 19, 2002.

* **Reprint requests and correspondence:** Dr. Jonathan D. Marmur, SUNY Health Science Center at Brooklyn, 450 Clarkson Avenue, Box 1257, Brooklyn, New York 11203, USA. jonathan@marmur.com

OBJECTIVES: This study was designed to compare the dose response of dalteparin versus unfractionated heparin (UFH) on the activated clotting time (ACT), and to determine whether the ACT can be used to monitor intravenous (IV) dalteparin during percutaneous coronary intervention (PCI).

BACKGROUND: The use of low molecular weight heparin (LMWH) during PCI has been limited by the presumed inability to monitor its anticoagulant effect using bedside assays.

METHODS: This study was performed in three phases. In vitro, ACTs were measured on volunteer (n = 10) blood samples spiked with increasing concentrations of dalteparin or UFH. To extend these observations in vivo, ACTs were then measured in patients (n = 15) who were sequentially treated with IV dalteparin and then UFH. Finally, a larger monitoring study was undertaken involving patients (n = 110) who received dalteparin 60 or 80 international U (IU)/kg alone or followed by abciximab. We measured ACT (Hemochron), activated partial thromboplastin time (aPTT), plasma anti-Xa and anti-IIa levels, tissue factor pathway inhibitor (TFPI) concentration, and plasma dalteparin concentration.

RESULTS: Dalteparin induced a significant rise in the ACT with a smaller degree of variance as compared to UFH. Five min after administration of IV dalteparin 80 IU/kg the ACT increased from 125 s (122 s, 129 s) to 184 s (176 s, 191 s) ($p < 0.001$). The aPTT, anti-Xa and anti-IIa activities, and TFPI concentration also demonstrated significant increases following IV dalteparin.

CONCLUSIONS: The ACT and aPTT are sensitive to IV dalteparin at clinically relevant doses. These data suggest that the ACT may be useful in monitoring the anticoagulant effect of intravenously administered dalteparin during PCI.

Introduction

Advantages of low molecular weight heparin (LMWH) over unfractionated heparin (UFH) include greater bioavailability (1), a decreased incidence of thrombocytopenia (2), and resistance to inactivation by platelet factor 4 (3). The greater bioavailability gives LMWH the potential for subcutaneous administration without the need for monitoring (4–6). This advantage has led to a significant increase in the use of LMWH in the management of unstable coronary syndromes.

Therefore an increasing number of patients referred for angiography and possible percutaneous coronary intervention (PCI) are arriving at the cardiac catheterization laboratory having received subcutaneous LMWH at various intervals from the time of subcutaneous injection. Though studies have demonstrated that LMWH can be used safely during PCI (7,8), an optimal strategy for the management of the anticoagulation of these patients has not been defined.

Current management of anticoagulation with UFH in the angioplasty setting uses the ACT to guide dosing (9,10). The ACT is a broadly used point-of-care assay, which appears to be sensitive to thrombin inhibition (11) and relatively insensitive to factor Xa inhibition (12). Because dalteparin is a LMWH that retains substantial anti-IIa activity (13), we hypothesized that the ACT would be sensitive to intravenous (IV) dalteparin at clinically relevant doses. Thus, the purpose of this study was 1) to compare the dose-response relationship between IV dalteparin and the ACT to the relationship between UFH and the ACT and 2) to determine whether the anticoagulant effects of IV dalteparin could be monitored during PCI by measuring the changes in the ACT.

Methods

The Institutional Review Board of the Mount Sinai Hospital, New York, NY, approved all protocols for this study. This study was performed in three phases. In the first phase, the effect of increasing concentrations of dalteparin on the ACT was studied and compared with changes induced by increasing concentrations of UFH in volunteer blood samples in vitro. To extend these observations in vivo and to allow for a paired comparison, the second phase of the study involved the generation of dose-response curves by sequentially administering dalteparin and UFH to the same patient. The third phase comprised a larger observational monitoring study in which patients undergoing cardiac catheterization or PCI were treated with dalteparin alone or dalteparin plus abciximab.

Comparative effects of dalteparin and UFH on the ACT in vitro. An in vitro comparative study was performed initially. This dose-response study used blood samples from 10 healthy volunteers (4 men and 6 women; mean age 39.4 ± 13.5 years). Twelve milliliters of blood were collected from each of the healthy volunteers, free of medication, via venipuncture of the antecubital vein using 21-gauge needles. Dalteparin (12,500 IU/ml) and UFH (1,000 USP U/ml) were both diluted with saline to 50 U/ml and added to aliquots of whole blood to achieve final concentrations of 0, 0.25, 0.5, 0.75, 1.0, and 1.25 U/ml. These concentrations were chosen because they yielded changes in the ACT that were within a clinically relevant range (125 to 296 s for UFH). These aliquots were immediately injected into CA510 tubes (International Technidyne, Edison, New Jersey) containing the activator Celite (diatomaceous earth) and agitated vigorously.

The CA510 tubes were then placed in the Hemochron 801 (International Technidyne, Edison, New Jersey) and the ACT was performed in duplicate. Results were recorded in seconds.

***In vivo* dose response**

To extend our observations *in vivo*, we compared the effects of 80 IU/kg of IV dalteparin to a standard interventional dose of IV UFH (70 U/kg). The key feature of this in vivo dose-response study was that dalteparin and UFH were given sequentially to the same patient, thereby allowing for a paired comparison. Fifteen patients (mean age 61.1 ± 10.1 years; 67% men) with a diagnosis of stable angina, asymptomatic with positive exercise stress test, unstable angina, non–Q-wave myocardial infarction (MI), or chest pain post-MI undergoing coronary angiography (n = 5) or PCI (n = 10) were enrolled after informed consent. The demographics of this study population are shown in Table 1. All patients undergoing PCI were given aspirin and clopidogrel before the procedure; abciximab was given to three of the 10 PCI patients at the discretion of the operator. Patients received a total of 80 IU/kg IV dalteparin administered in two separate boluses of 40 IU/kg each at baseline and at 5 min. After a washout period of at least 12 h, a total of 70 U/kg IV UFH was administered as a split bolus of 40 U/kg and 30 U/kg at baseline and at 5 min, respectively. Blood samples were drawn at baseline, and 5 and 10 min after IV drug administration from the arterial access sheath (dalteparin) or antecubital vein (UFH) into vacutainers containing one volume 3.8% sodium citrate (Becton Dickinson, Franklin Lakes, New Jersey). The anticoagulant effects of both IV dalteparin and UFH were assessed by measuring the ACT, activated partial thromboplastin time (aPTT), anti-Xa levels, and anti-IIa levels.

Monitoring study

On the basis of the observations from the in vitro and in vivo dose-response studies, we undertook an observational monitoring study in which patients were given either 60 or 80 IU/kg IV dalteparin. In this phase of the study, there was no UFH comparator arm.

Patient population

The study population was derived from patients with a diagnosis of stable angina, asymptomatic with positive exercise stress test, unstable angina, non–Q-wave MI, or chest pain post-MI undergoing cardiac catheterization at Mount Sinai Hospital, New York, New York. A total of 110 patients were enrolled over an eight-month period (4/00 to 12/00). Of the 110 patients, 24 (22%) underwent coronary angiography and 86 (78%) underwent PCI. The demographics of the monitoring study population are shown in Table 1. A diagram of patient flow is shown in Figure 1. Informed consent was obtained from each patient before enrollment.

Exclusion criteria for the *in vivo* dose response and monitoring studies included MI within 24 h, active internal bleeding, recent (within six weeks) gastrointestinal or genitourinary bleeding of clinical significance, history of cerebrovascular accident (CVA) within two years or CVA with a residual neurologic deficit, bleeding diathesis, administration of oral anticoagulant within seven days unless prothrombin time was <1.2 times control, thrombocytopenia (<100,000/µl), recent (within six weeks) major surgery or trauma, intracranial neoplasm, arteriovenous malformation or aneurysm, severe uncontrolled hypertension >180/100 mm Hg on enrollment to the study, use of IV dextran before PCI, or hypersensitivity to one of the study drugs or their components. Because excretion of dalteparin is predominantly renal, patients with creatinine ≥2.0 were also excluded.

Enrolled patients being treated with IV UFH had their infusion of UFH discontinued at least 4 h before catheterization. Patients too unstable to allow for heparin cessation on call to the cardiac catheterization laboratory were excluded. Patients with a baseline ACT ≥160 s were excluded because an ACT above this level was likely due to residual heparin effect that could confound the analysis of dalteparin's effect on the indices of coagulation. Patients who had received subcutaneous dalteparin (n = 8) before catheterization were not excluded on the basis of the initial ACT. In these patients, an ACT >160 s mandated a reduced dose (40 IU/kg) of dalteparin.

Study medications

The effects of ACT, aPTT, and other coagulation parameters were studied using two doses of IV dalteparin (60 IU/kg or 80 IU/kg), with and without abciximab. The initial 52 consecutive patients received 60 IU/kg IV dalteparin, and the subsequent 50 consecutive patients received 80 IU/kg IV dalteparin. An initial dose of 60 IU/kg was selected on the basis of previously published data (14). The dose of 80 IU/kg was chosen on the basis of a 20 IU/kg increment (40 IU/kg to 60 IU/kg) used in the aforementioned study by Kereiakes et al. (14).

A total of 110 patients received IV dalteparin. Of the 110 patients receiving IV dalteparin, 52 (47%) received a dose of 60 IU/kg. Thirty-four of these 52 patients (65%) also received abciximab (0.25 mg/kg bolus and 0.125 µg/kg/h maintenance infusion). Of the 110 patients receiving IV dalteparin, 50 (46%) received a dose of 80 IU/kg. Twenty-four of these 50 patients (48%) also received abciximab. Abciximab was given at the operator's discretion and was administered after the 10 min blood draw. All patients undergoing PCI were given aspirin and clopidogrel before the procedure.

Subcutaneous substudy

Of the 110 patients, eight received a single subcutaneous injection of dalteparin 120 IU/kg during the noninvasive phase of their hospital course. Using data from the dose-response study, it was arbitrarily decided that immediately before PCI patients with an ACT >160 s (n = 2) were to receive an IV dalteparin 40 IU/kg bolus and patients with ACT <160 s (n = 6) were to receive an IV dalteparin 60 IU/kg bolus. Four of the eight patients received abciximab (0.25 mg/kg bolus and 0.125 μg/kg/h maintenance infusion) 10 min after dalteparin at the operator's discretion.

Blood samples

Six blood samples were collected from the arterial access sheath in sodium citrate vacutainers at the following time points: baseline and 5, 10, 20, 40, and 60 min after IV dalteparin in the observational monitoring study. Patients in the subcutaneous substudy had their blood samples drawn directly from the antecubital vein at baseline and then every hour following dalteparin subcutaneous administration until the time of the procedure. Blood samples were centrifuged at 3,000 *g* for 15 min at 22°C. Platelet-poor plasma was collected and aliquoted into 2 ml eppendorf tubes and stored at –70°C. Frozen samples were transported on dry ice to the Thrombosis and Hemostasis Research Laboratory at Loyola Medical Center (Maywood, Illinois). Arterial access sheaths were removed 2 to 4 h after completion of the procedure.

Monitoring of the anticoagulant effect

ACT. Two milliliters of blood was collected in a FTCA510 tube (International Technidyne, Edison, New Jersey) with the activator Celite. The tube was vigorously shaken and placed in the Hemochron 8000 (International Technidyne, Edison, New Jersey). Results were recorded in seconds.

aPTT. Samples were analyzed using STA-PTT A 5, a reagent containing rabbit cerebral cephalin and silica (Diagnostica Stago, Asnieres-Sur-Seine, France) on the STA-R (Diagnostica Stago, Gennevilliers, France). Results were recorded in seconds.

Antiprotease assays. Both the anti-Xa (15) and anti-IIa (16) assays were performed as previously described. Anti-Xa and anti-IIa activities were both adjusted to a reference baseline value of 0.0 IU/ml in all cohorts.

Heptest assay. Heptest was performed on a fibrometer, according to Yin et al. (17). Heptest activity was adjusted to a reference baseline value of 0.0 IU/ml in all cohorts.

Quantification of TFPI

A tissue factor pathway inhibitor (TFPI) enzyme linked immunoabsorbent spectrophotometric assay was performed (18,19). Results were expressed as nanograms/milliliter.

Assessment of safety

Minor and major bleeding was defined according to the criteria used by the Thrombolysis in Myocardial Infarction (TIMI) Trial (20). Severe thrombocytopenia was defined by a platelet count below 50,000/µl. Mild thrombocytopenia was defined as a platelet count below 100,000/µl or a count below 50% of the baseline value. The degree of thrombocytopenia was assessed postprocedurally after either dalteparin alone or combination dalteparin and abciximab therapy. Myocardial infarction was defined as an elevation in CK-MB three times the upper limit of normal. Blood for CK-MB analysis was drawn before PCI and every 8 h for 24 h.

Statistical analysis

Patient demographic and coagulation parameter data were described using mean (95% confidence interval) and mean ± SD where indicated. Analysis of variance was used to compare the effect on coagulation parameters across the six sampling time points for each dose of dalteparin, 60 IU/kg and 80 IU/kg. Normality was tested using the Shapiro-Wilkes test for small samples. All data passed normality with the exception of the ACT data from the sequential dalteparin and UFH group, which were transformed using logarithms and retested. The variability of the ACT response to dalteparin and UFH were determined by calculating the coefficient of variance (mean/SD x 100) for both drugs in the in vitro and in vivo dose-response studies. To determine whether these variations were similar, an F test was performed as previously described (21). All statistical analyses were performed using SPSS version 10.0. A two-tailed $p < 0.05$ was considered statistically significant.

Results

Comparative effects of dalteparin and UFH on the ACT *in vitro*.

Dalteparin and UFH both demonstrated a significant dose response with respect to the ACT (Fig. 2). Although a greater slope was seen with UFH, a moderate slope was present in the dalteparin-induced curve. The degree of variability in ACT at the highest concentration (1.25 U/ml) as measured by the coefficient of variance was numerically, but not statistically, lower for dalteparin than for UFH (8.5 vs. 11.4; $p = 0.26$).

Comparative effects of dalteparin and UFH on the ACT *in vivo*

As was seen in the in vitro experiments, a significant rise in ACT was discernible as the dose of both dalteparin and UFH was increased in vivo (Fig. 3). The ACT of patients receiving 80 IU/kg dalteparin demonstrated a significantly lower coefficient of variance as compared to patients receiving 70 U/kg UFH (12.5 vs. 23.6; $p = 0.03$).

After the boluses of dalteparin and UFH were administered, the ACT, aPTT, anti-Xa activity, and anti-IIa activity all increased (Table 2). The increases observed in the ACT after dalteparin administration from samples drawn at the 5 and 10 min time points demonstrated a significant but weak correlation to the elevations in anti-Xa ($r = 0.47$; $p = 0.01$) and anti-IIa activities ($r = 0.37$; $p = 0.048$). After UFH administration numerically weaker correlations were seen between the increases in the ACT and the elevations in anti-Xa ($r = 0.06$; $p = 0.75$) and anti-IIa activities ($r = 0.26$; $p = 0.18$) from samples collected at the 5- and 10-min time points.

Monitoring study

Response of coagulation parameters to IV dalteparin

The changes in coagulation parameters for the 102 patients in the monitoring study who received IV dalteparin without pretreatment with subcutaneous dalteparin are listed in Table 3. Following IV dalteparin 60 or 80 IU/kg, there was a significant elevation in the ACT at 5 min ($p < 0.001$) and throughout the 60-min observation period ($p < 0.001$).

A rise in the ACT of at least 20% from baseline values was seen in every patient studied. In comparison to 60 IU/kg, an 80 IU/kg IV dose of dalteparin led to a significantly greater elevation in the ACT that was sustained throughout the 60-min observation period ($p < 0.001$).

Similar trends were seen in the aPTT, in the plasma levels of anti-Xa and anti-IIa activity, and Heptest (Table 3). These trends were also present in the group of patients who were treated with dalteparin alone (Fig. 4). Note that in this group of patients, a numerical decline in the ACT at 60 min was noted in comparison to the peak levels at 10 min (156 vs. 167 s for 60 IU/kg dose, $p = 0.09$; 175 vs. 187 s for the 80 IU/kg dose, $p = 0.10$).

The ACT and aPTT values generated from samples drawn at baseline and 5 min post-dalteparin were correlated ($r = 0.82$; $p < 0.001$). Elevations in anti-Xa and anti-IIa activity were weakly correlated with changes in the ACT ($r = 0.26$; $p = 0.012$ and $r = 0.31$; $p = 0.002$, respectively).

Response to subcutaneous dalteparin administration

Eight patients in the study received subcutaneous dalteparin 120 IU/kg at least 2 h before PCI. There was an increase in ACT from a baseline of 126 ± 10 s to 146 ± 11 s at 1 h, with a peak value of 151 ± 13 s at 2 h ($p < 0.001$). Similarly, aPTT rose from a baseline of 28.2 ± 2.5 s to 36.6 ± 6.1 s at 1 h ($p < 0.001$) and to 38.7 ± 5.8 s at 2 h ($p < 0.001$). Anti-Xa activity increased to 0.56 ± 0.24 IU/ml at 1 h and 0.70 ± 0.18 IU/ml at 2 h ($p < 0.001$).

These patients received IV dalteparin 40 IU/kg (n = 2) or 60 IU/kg (n = 6) during PCI depending on the ACT measured immediately after sheath insertion. In those patients receiving IV dalteparin 40 IU/kg, 5 min after the IV bolus the ACT increased from 160 ± 1 s to 220 ± 10 s; aPTT increased from 42.2 ± 13.3 s to 71.6 ± 10.7 s and anti-Xa activity increased from 0.79 ± 0.4 IU/ml to 1.21 ± 0.4 IU/ml. In those patients receiving IV dalteparin 60 IU/kg at 5 min after the IV bolus, the ACT increased from 141 ± 13 s to 172 ± 20 s ($p < 0.001$); aPTT increased from 36.7 ± 2.6 s to 76.3 ± 12.2 s ($p < 0.001$) and anti-Xa activity increased from 0.71 ± 0.26 IU/ml to 1.79 ± 0.64 IU/ml ($p = 0.006$).

Safety outcomes

Death, MI, and urgent revascularization

There was no death or urgent revascularization during the hospital course of the study population. Two of the 96 PCI patients patient had MI (2.1%).

Bleeding rates in patients undergoing PCI

One patient in the IV dalteparin 80 IU/kg and abciximab cohort suffered major bleeding requiring transfusion, yielding a major bleeding rate of 1.0% (1/96). Two patients in the IV dalteparin 80 IU/kg and abciximab cohort and one each in the *in vivo* dose-response study and subcutaneous dalteparin 120 IU/kg cohort had minor bleeding, yielding a minor bleeding rate of 4.2% (4/96). No patients with minor bleeding required blood transfusion.

Episode of thrombocytopenia

One patient in the IV dalteparin 80 IU/kg and abciximab cohort experienced an episode of severe thrombocytopenia with no sequelae. There were no episodes of mild thrombocytopenia.

Discussion

This is the first study to prospectively analyze the effects of IV dalteparin on the ACT. Our findings suggest that the ACT may constitute a reliable assay for monitoring dalteparin during PCI for the following reasons. First, the elevation is significant and rapidly detectable; within 5 min of receiving IV dalteparin 80 IU/kg, the ACT increased on average 59 s (Table 3). Second, there is a highly significant dose-response relationship *in vitro* (r = 0.99) (Fig. 2) and *in vivo* (r = 0.76) (Fig. 3). A dose response is also demonstrated by the fact that patients receiving IV dalteparin 80 IU/kg experienced a significantly greater rise in their ACT in comparison with those receiving 60 IU/kg. Third, in comparison to the rise in the ACT induced by UFH, there appears to be less variance in the dalteparin-induced elevations in the ACT both in vitro and in vivo. Fourth, the increase in ACT was sustained for a period of time relevant to current interventional practice (40 min, with a decline in values at approximately 60 min for patients treated with dalteparin alone). This raises the possibility that a decline in the ACT to a targeted level (for example, <150 s) could potentially be used to determine the timing of sheath removal. Finally, these observations are consistent with previous reports. In a study by Kereiakes et al. (14), patients treated with either 40 IU/kg or 60 IU/kg of dalteparin IV achieved mean ACTs 30 min after administration of 166 ± 28 s and 180 ± 38 s, respectively. Similarly, in a study using IV enoxaparin during PCI the mean ACT increased from 130 ± 19 to 188 ± 29 s 5 min after administration (7). These previously reported data support the notion that the ACT may be useful in monitoring the effects of intravenously administered LMWH.

To determine whether the elevation seen in the ACT following IV dalteparin occurred in isolation or in conjunction with changes in other indices of anticoagulation, the aPTT, plasma anti-Xa and anti-IIa activities, and TFPI concentration were also measured. The aPTT rose significantly after IV dalteparin administration and to a level traditionally regarded as therapeutic in the context of medical management for unstable angina (1.5- to 2-fold above baseline) (22). The aPTT demonstrated a significant correlation (r = 0.82) with the ACT, supporting the notion that the elevated ACT values post-dalteparin reflected an anticoagulated state. Studies have shown both the ACT and aPTT to be prolonged by direct thrombin inhibitors (11,23) and to be relatively insensitive to Factor Xa inhibition (12,24). These observations suggest that the rise in the ACT documented in the present study was more likely due to dalteparin's anti-IIa activity than to its anti-Xa activity. A theoretic advantage of factor IIa inhibition, versus factor Xa inhibition, is that inhibition of thrombin may prevent feedback activation of factors V and VIII (25,26).

Our findings of poor correlations between the ACT and anti-Xa and anti-IIa activities indicate that dalteparin-induced changes in the ACT cannot be accounted for solely on the basis of dalteparin's anti-Xa and anti-IIa effects. Despite the poor correlation in this study between the ACT and plasma anti-Xa and anti-IIa activities, as well as ambiguity in the literature regarding a correlation between the ACT and anti-Xa activity in UFH-treated patients (27,28), monitoring of UFH with the ACT to achieve target levels between 200 and 300 s has become a generally accepted standard in interventional practice (29). Furthermore, unlike anti-Xa and anti-IIa levels, the ACT has been correlated to clinical outcomes (10,30). One explanation for the observation that the ACT appears to correlate better to clinical outcomes than to specific levels of factor Xa or IIa inhibition is that the ACT is influenced by a variety of factors that collectively determine the blood's propensity to thrombose. For example, antiplatelet agents have been noted to increase the ACT (31). In addition, both dalteparin and UFH affect the coagulation mechanism at multiple levels. Antithrombin (whether potentiated by LMWH or UFH) not only exerts anti-Xa and anti-IIa effects, but also has been shown to inhibit factors XIIa (32), XIa (33,34), and IXa (35,36) of the intrinsic coagulation pathway. These agents also induce the release of TFPI (37) and may alter the inducibility of tissue factor on monocytes, thereby providing additional mechanisms to retard thrombus formation. Seen in this light, it is hardly surprising that weak correlations were found between the ACT and specific anti-Xa and anti-IIa levels.

Others have proposed that rather than using the ACT, the effects of LMWH in patients undergoing PCI would be better gauged by measuring anti-Xa levels (28,38). However, these observations pertain to LMWH administered subcutaneously and to a specific formulation, enoxaparin, that has a diminished anti-IIa effect in comparison to dalteparin (13). Moreover, measurement of anti-Xa activity would assess the action of LMWH on an isolated (albeit important) step of the cascade, but would not take into account the multiple levels at which a LMWH acts (factors XIIa, XIa, IXa, and TFPI as noted earlier). Additionally, to our knowledge previous clinical studies have demonstrated only weak correlations between anti-Xa levels and thrombus formation (39,40), and reported conflicting data on the relationship between anti-Xa levels and the incidence of hemorrhage (40–42). In contrast, a recent study by Chew et al. demonstrated a significant relationship between the ACT and ischemic/bleeding events after PCI in patients receiving UFH (10). Furthermore, anti-Xa assays used for monitoring display interassay variability depending on assay technique (43) or type (44) and are not readily available as a bedside device. Thus, it should not be assumed a priori that anti-Xa activity monitoring would be superior to monitoring the ACT in patients receiving intravenous LMWH.

Point-of-care monitoring of the effects of LMWH may be particularly important in patients with morbid obesity or renal dysfunction (26,45,46), two populations in whom rigorous dosing studies have not been reported (46). Additional benefits of monitoring may include detection of errors in IV administration (47) and the potential for dose adjustment in patients receiving antithrombotic, fibrinolytic, or antiplatelet therapy before PCI.

Study limitations. There are several limitations associated with the study. First, ACTs were measured using the Hemochron system, and thus our data may not be readily extrapolated to the Hemotech system (Medtronic, Parker, Colorado) used in many cardiac catheterization laboratories. Second, the study design was nonrandomized and open label. Third, there was no comparator arm with heparin alone in the monitoring study. Fourth, abciximab was the lone adjunctive glycoprotein IIb/IIIa inhibitor used, and therefore the results may not apply to patients receiving eptifibatide or tirofiban. Fifth, our findings may not be generalized to all LMWHs; the effect of dalteparin on the ACT, aPTT, and other tests may differ from other LMWH agents because of differences in the ratios of anti-Xa:anti-IIa activity. The lower anti-Xa:anti-IIa ratio for dalteparin compared to enoxaparin (2.7 vs. 3.8), for example, may result in greater sensitivity of anti-IIa dependent tests for dalteparin than for enoxaparin. Finally, blood samples were collected for only 60 min after the initial dalteparin bolus, thereby limiting the study temporally. A longer period of sampling may have helped to delineate the duration of the anticoagulated state induced by dalteparin.

In conclusion, the ACT and aPTT are sensitive to IV dalteparin at clinically relevant doses. These data suggest that the ACT may have the potential to be integrated into an IV dalteparin monitoring strategy. The ability to monitor dalteparin may facilitate the use of LMWH in PCI and in other invasive procedures such as coronary artery bypass surgery.

References

1. Hirsh J, Levine MN. Low molecular weight heparin. *Blood*. 1992;79:1–17[Free Full Text]

2. Warkentin TE, Levine MN, Hirsh J, et al. Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. *N Engl J Med*. 1995;332:1330–1335[Abstract/Free Full Text]

3. Padilla A, Gray E, Pepper DS, Barrowcliffe TW. Inhibition of thrombin generation by heparin and low molecular weight (LMW) heparins in the absence and presence of platelet factor 4 (PF4). *Br J Haematol*. 1992;82:406–413[Medline]

4. Fragmin during Instability in Coronary Artery Disease (FRISC) study group. Low-molecular-weight heparin during instability in coronary artery disease. *Lancet*. 1996;347:561–568[CrossRef][Medline]

5. Klein W, Buchwald A, Hillis SE, et al. Comparison of low-molecular-weight heparin with unfractionated heparin acutely and with placebo for 6 weeks in the management of unstable coronary artery disease. Fragmin in unstable coronary artery disease study (FRIC). *Circulation*. 1997;96:61–68[Abstract/Free Full Text]

6. Cohen M, Demers C, Gurfinkel EP, et al. Low-molecular-weight heparins in non-ST-segment elevation ischemia: the ESSENCE trial. Efficacy and Safety of Subcutaneous Enoxaparin versus intravenous unfractionated heparin, in non–Q-wave Coronary Events. *Am J Cardiol*. 1998;82:19–24L

7. Rabah MM, Premmereur J, Graham M, et al. Usefulness of intravenous enoxaparin for percutaneous coronary intervention in stable angina pectoris. *Am J Cardiol*. 1999;84:1391–1395[CrossRef][Medline]

8. Kereiakes DJ, Fry E, Matthai W, et al. Combination enoxaparin and abciximab therapy during percutaneous coronary intervention: "NICE guys finish first". *J Invasive Cardiol*. 2000;12(Suppl A):1–5A[Medline]

9. Rath B, Bennett DH. Monitoring the effect of heparin by measurement of activated clotting time during and after percutaneous transluminal coronary angioplasty. *Br Heart J*. 1990;63:18–21[Abstract/Free Full Text]

10. Chew DP, Bhatt DL, Lincoff AM, et al. Defining the optimal activated clotting time during percutaneous coronary intervention: aggregate results from 6 randomized, controlled trials. *Circulation*. 2001;103:961–966[Abstract/Free Full Text]

11. Topol EJ, Bonan R, Jewitt D, et al. Use of a direct antithrombin, hirulog, in place of heparin during coronary angioplasty. *Circulation*. 1993;87:1622–1629[Abstract/Free Full Text]

12. Vuillemenot A, Schiele F, Meneveau N, et al. Efficacy of a synthetic pentasaccharide, a pure factor Xa inhibitor, as an antithrombotic agent—a pilot study in the setting of coronary angioplasty. *Thromb Haemost*. 1999;81:214–220[Medline]

13. Eriksson BI, Soderberg K, Widlund L, Wandeli B, Tengborn L, Risberg B. A comparative study of three low-molecular weight heparins (LMWH) and unfractionated heparin (UH) in healthy volunteers. *Thromb Haemost*. 1995;73:398–401[Medline]

14. Kereiakes DJ, Kleiman NS, Fry E, et al. Dalteparin in combination with abciximab during percutaneous coronary intervention. *Am Heart J*. 2001;141:348–352[CrossRef][Medline]

15. Walenga JM, Bara L, Samama MM, Fareed J. Amidolytic antifactor Xa assays in the laboratory evaluation of heparin and low molecular weight fractions. *Semin Thromb Hemost*. 1985;11:100–107[Medline]

16. Walenga JM, Fareed J, Hoppensteadt D, Emanuele RM. In vitro evaluation of heparin fractions: old vs. new methods. *Crit Rev Clin Lab Sci*. 1986;22:361–389[Medline]

17. Yin ET, Wessler S, Butler JV. Plasma heparin: a unique, practical, submicrogram-sensitive assay. *J Lab Clin Med*. 1973;81:298–310[Medline]

18. Hubbard AR, Jennings CA. Inhibition of the tissue factor-factor VII complex: involvement of factor Xa and lipoproteins. *Thromb Res*. 1987;46:527–537[CrossRef][Medline]

19. Broze GJ, Warren LA, Novotny WF, Higuchi DA, Girard JJ, Miletich JP. The lipoprotein-associated coagulation inhibitor that inhibits the factor VII-tissue factor complex also inhibits factor Xa: insight into its possible mechanism of action. *Blood*. 1988;71:335–343[Abstract/Free Full Text]

20. Rao AK, Pratt C, Berke A, et al. Thrombolysis in Myocardial Infarction (TIMI) Trial—phase I: hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. *J Am Coll Cardiol*. 1988;11:1–11[Abstract]

21. Zar JH. Biostatistical Analysis. 3rd edition. Saddle River, NJ: Prentice-Hall, Inc

22. Cairns JA, Theroux P, Lewis HD Jr, Ezekowitz M, Meade TW, Sutton GC. Antithrombotic agents in coronary artery disease. *Chest*. 1998;114:611–633S

23. Klootwijk P, Lenderink T, Meij S, et al. Anticoagulant properties, clinical efficacy and safety of efegatran, a direct thrombin inhibitor, in patients with unstable angina. *Eur Heart J*. 1999;20:1101–1111[Abstract/Free Full Text]

24. Heran C, Morgan S, Kasiewski C, et al. Antithrombotic efficacy of RPR208566, a novel factor Xa inhibitor, in a rat model of carotid artery thrombosis. *Eur J Pharmacol*. 2000;389:201–207[CrossRef][Medline]

25. Ofosu FA, Hirsh J, Esmon CT, et al. Unfractionated heparin inhibits thrombin-catalysed amplification reactions of coagulation more efficiently than those catalysed by factor Xa. *Biochem J*. 1989;257:143–150[Medline]

26. Weitz JI. Low-molecular-weight heparins. *N Engl J Med*. 1997;337:688–698[Free Full Text]

27. Despotis GJ, Summerfield AL, Joist JH, et al. Comparison of activated coagulation time and whole blood heparin measurements with laboratory plasma anti-Xa heparin concentration in patients having cardiac operations. *J Thorac Cardiovasc Surg*. 1994;108:1076–1082[Abstract/Free Full Text]

28. Henry TD, Satran D, Knox LL, Iacarella CL, Laxson DD, Antman EM. Are activated clotting times helpful in the management of anticoagulation with subcutaneous low-molecular-weight heparin? *Am Heart J*. 2001;142:590–593[CrossRef][Medline]

29. The ESPRIT Investigators. Novel dosing regimen of eptifibatide in planned coronary stent implantation (ESPRIT): a randomised, placebo-controlled trial. *Lancet*. 2000;356:2037–2044[CrossRef][Medline]

30. Narins CR, Hillegass WB Jr, Nelson CL, et al. Relation between activated clotting time during angioplasty and abrupt closure. *Circulation*. 1996;93:667–671[Abstract/Free Full Text]

31. Moliterno DJ, Califf RM, Aguirre FV, et al. Effect of platelet glycoprotein IIb/IIIa integrin blockade on activated clotting time during percutaneous transluminal coronary angioplasty or directional atherectomy (the EPIC trial). Evaluation of c7E3 Fab in the Prevention of Ischemic Complications trial. *Am J Cardiol*. 1995;75:559–562[CrossRef][Medline]

32. Holmer E, Kurachi K, Soderstrom G. The molecular-weight dependence of the rate-enhancing effect of heparin on the inhibition of thrombin, factor Xa, factor IXa, factor XIa, factor XIIa and kallikrein by antithrombin. *Biochem J*. 1981;193:395–400[Medline]

33. Soons H, Janssen-Claessen T, Tans G, Hemker HC. Inhibition of factor XIa by antithrombin III. *Biochemistry*. 1987;26:4624–4629[CrossRef][Medline]

34. Mauron T, Lammle B, Wuillemin WA. Influence of low molecular weight heparin and low molecular weight dextran sulfate on the inhibition of coagulation factor XIa by serpins. *Thromb Haemost*. 1998;80:82–86[Medline]

35. Pieters J, Lindhout T, Willems G. Heparin-stimulated inhibition of factor IXa generation and factor IXa neutralization in plasma. *Blood*. 1990;76:549–554[Abstract/Free Full Text]

36. Mauray S, de Raucourt E, Talbot JC, Dachary-Prigent J, Jozefowicz M, Fischer AM. Mechanism of factor IXa inhibition by antithrombin in the presence of unfractionated and low molecular weight heparins and fucoidan. *Biochim Biophys Acta*. 1998;1387:184–194[CrossRef][Medline]

37. Fareed J, Jeske W, Hoppensteadt D, Clarizio R, Walenga JM. Are the available low-molecular-weight heparin preparations the same? *Semin Thromb Hemost*. 1996;22:77–91

38. Collet JP, Montalescot G, Lison L, et al. Percutaneous coronary intervention after subcutaneous enoxaparin pretreatment in patients with unstable angina pectoris. *Circulation*. 2001;103:658–663[Abstract/Free Full Text]

39. Leizorovicz A, Bara L, Samama MM, Haugh MC. Factor Xa inhibition: correlation between the plasma levels of anti-Xa activity and occurrence of thrombosis and haemorrhage. *Haemostasis*. 1993;23(Suppl 1):89–98

40. Bara L, Planes A, Samama MM. Occurrence of thrombosis and haemorrhage, relationship with anti-Xa, anti-IIa activities, and D-dimer plasma levels in patients receiving a low molecular weight heparin, enoxaparin or tinzaparin, to prevent deep vein thrombosis after hip surgery. *Br J Haematol*. 1999;104:230–240[CrossRef][Medline]

41. Nieuwenhuis HK, Albada J, Banga JD, Sixma JJ. Identification of risk factors for bleeding during treatment of acute venous thromboembolism with heparin or low molecular weight heparin. *Blood*. 1991;78:2337–2343[Abstract/Free Full Text]

42. The Thrombolysis in Myocardial Infarction (TIMI) 11A Trial Investigators. Dose-ranging trial of enoxaparin for unstable angina: results of TIMI 11A. *J Am Coll Cardiol*. 1997;29:1474–1482[Abstract]

43. Kitchen S, Iampietro R, Woolley AM, Preston FE. Anti Xa monitoring during treatment with low molecular weight heparin or danaparoid: inter-assay variability. *Thromb Haemost*. 1999;82:1289–1293[Medline]

44. Depasse F, Gilbert M, Goret V, Rolland N, Samama MM. Anti-Xa monitoring: inter-assay variability. *Thromb Haemost*. 2000;84:1122–1123[Medline]

45. Abbate R, Gori AM, Farsi A, Attanasio M, Pepe G. Monitoring of low-molecular-weight heparins in cardiovascular disease. *Am J Cardiol*. 1998;82:33–36L

46. Hirsh J, Warkentin TE, Shaughnessy SG, et al. Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. *Chest*. 2001;119:64–94S

47. Teahon K, Bateman DN. A survey of intravenous drug administration by preregistration house officers. *BMJ*. 1993;307:605–606[Medline]

[Footnotes, Acknowledgements, Tables and Figures omitted.]

To appreciate the potential use of monitoring tests for the use of Lovenox, the following article reviews the available studies at the time when this patient was treated:

http://ndt.oxfordjournals.org/cgi/content/full/19/6/1552

Nephrol Dial Transplant (2004) 19: 1552-1558

NDT Advance Access originally published online on March 19, 2004

Factor Xa-activated whole blood clotting time (Xa-ACT) for bedside monitoring of dalteparin anticoagulation during haemodialysis

Rolf Dario Frank, Vincent M. Brandenburg, Regina Lanzmich and Jürgen Floege

Department of Nephrology and Clinical Immunology, University Hospital Aachen, Germany

Correspondence and offprint requests to: Rolf Dario Frank, MD, Department of Nephrology, University Hospital Aachen, D-52057 Aachen, Germany. Email: dario.frank@ukaachen.de

Abstract

Background. Low molecular weight heparins (LMWH) like dalteparin are increasingly used for anticoagulation during haemodialysis (HD). The available laboratory tests for monitoring LMWH anticoagulation are time-consuming and expensive, and the suitability of the conventional activated clotting time (ACT) is controversial. A simple and cheap bedside test would be useful.

Methods. We studied the factor Xa-activated whole blood clotting time (Xa-ACT) *in vitro* and *in vivo* in nine patients undergoing chronic HD with i.v. dalteparin bolus anticoagulation and compared it with the conventional ACT. Plasma anti-factor Xa (antiXa) activity was determined with a chromogenic assay. Thrombin–antithrombin complexes were measured to detect coagulation activation.

Results. Xa-ACT and ACT were prolonged with rising dalteparin concentration. *In vitro*, both clotting times were strongly correlated with the antiXa levels ($r = 0.94$ and 0.89, respectively). Nevertheless, compared with the ACT, the Xa-ACT was considerably more sensitive to the LMWH *in vitro* (healthy blood: Xa-ACT 90 s/U *vs* ACT 26 s/U; uraemic blood: Xa-ACT 96 s/U *vs* ACT 31 s/U) as well as *in vivo* (Xa-ACT 81 s/U *vs* ACT 22 s/U) and reflected different intensities of anticoagulation.

An initial dalteparin bolus of 80±11 U/kg body weight was able to prevent coagulation activation for up to 4 h of HD.

Conclusion. For monitoring LMWH anticoagulation the Xa-ACT was superior to the conventional ACT *in vitro* as well as *in vivo* during HD. The Xa-ACT can be useful as a LMWH bedside test. The ACT was not sensitive enough to serve as a LMWH monitoring tool.

Introduction

During haemodialysis (HD) or haemofiltration anticoagulation is required to prevent coagulation activation and clot formation in the extracorporeal circuit. The majority of the HD patients are still treated with unfractionated heparin (UFH). For point-of-care monitoring of UFH the activated whole blood clotting time (ACT) is commonly used as bedside test [1–3].

Recently, low molecular weight heparins (LMWH) like dalteparin have been increasingly used for anticoagulation during HD and were shown to be safe and convenient anticoagulants. In long-term use, LMWH offer several advantages compared with UFH including beneficial effects on serum lipids, factor VIII and bone density, less impact on platelet function [4–6], lower incidence of HIT type II [7] and fewer bleeding complications [8]. Furthermore, the prolonged half-life of LMWH allows simplified dosing with application as a single initial bolus [9,10]. For patients prone to bleeding complications, a continuous infusion is recommended to avoid high peak plasma levels. LMWH dosage recommendations are primarily based on the body weight, but since dosage requirements vary considerably between individuals and also may change due to co-morbidity, bleeding risk or dialysis modalities [11,12], the LMWH dosage has to be adapted individually and to the current clinical conditions in order to avoid over- or under-treatment.

In contrast to UFH, the antithrombotic effect of LMWHs is mediated mainly by inhibition of activated factor X, whereas the anti-factor IIa activity is less important. Since LMWHs only slightly prolong standard coagulation assays (aPTT, thrombin time), anticoagulation with LMWHs is almost exclusively monitored by a chromogenic substrate assay measuring the anti-factor Xa (antiXa) activity. This method requires a specialized coagulation laboratory and is therefore not generally available. Furthermore, the assay is expensive and time-consuming.

A simple and rapid bedside test, which reliably reflects the extent of LMWH anticoagulation, would be helpful for initial dose titration, dose adjustments and checking the delivered drug amount. The usefulness of the conventional ACT for LMWH monitoring is still under debate and available data are conflicting [13–17].

In 1998, Mori *et al*. reported a modification of the ACT, called Xa-ACT, using bovine factor Xa as an activating agent instead of siliceous earth, which might serve as a bedside test for LMWH monitoring [18]. As the authors did not report antiXa levels and used a continuous infusion regimen achieving constant antiXa levels, the available data do not allow us to draw firm conclusions regarding the suitability of this test.

Therefore, we evaluated the Xa-ACT, adapted to the Trimed ACTester®, *in vitro* and in patients undergoing chronic HD with dalteparin bolus anticoagulation and compared it with the conventional ACT.

Subjects and Methods

Patients

Nine stable patients (three males, six females, mean age±SD, 61±15 years, range 34–80 years, mean body dry weight±SD, 64.8±15.2 kg, range 43–98 kg) from the University Hospital dialysis unit were included. All patients had end-stage renal failure and were undergoing uneventful intermittent HD (five patients) or haemodiafiltration (HDF) (four patients) with dalteparin anticoagulation three times a week for >6 months. The coagulation studies were done during a midweek session after a short dialysis-free interval. As vascular access, arteriovenous native forearm fistulae (seven patients) or fistulae with PTFE interponates (two patients) were used.

Before participation, all patients were evaluated by physical examination and laboratory tests (full blood count, liver enzymes, total protein, serum protein electrophoresis, C-reactive protein, prothrombin time, activated partial thromboplastin time, antithrombin activity and fibrinogen).

Exclusion criteria were acute infectious or autoimmune diseases, known malignancy, haemorrhagic or thrombotic coagulation disorders, need for long-term anticoagulation, surgery or blood transfusion during the last 2 weeks and abnormal findings in one or more parameters of the laboratory screening.

The study was approved by the ethics committee of the University Hospital Aachen and informed consent was obtained from all patients.

Dialysis procedure

HD was performed in two patients using the Genius® therapy system (Fresenius Medical Care, Bad Homburg, Germany) and in three patients with the MTS 4008 E (Fresenius). For HDF (four patients) the AK 100 Ultra from Gambro (Hechingen, Germany) was employed.

The following dialyser resp. haemofilter types were used: F7 HPS (low-flux polysulfone, Fresenius Medical Care, four patients), Polyflux 14 S (high-flux polyamide membrane, Gambro, Hechingen, Germany, three patients), Tricea 190 G (cellulose triacetate, Baxter, Illinois, USA, one patient) and Arylane H9 (Polyarylethersulfone, Hospal, one patient). Dialyzate resp. substitution fluids were bicarbonate-buffered. The extracorporeal systems were primed with isotonic saline without anticoagulant. Blood flow was kept between 200 and 300 ml/min (mean±SD, 252±37 ml/min). The duration of the HD or HDF treatment sessions was 4–5 h (mean±SD, 4.4±0.4 h).

Anticoagulation

The patients were anticoagulated with the LMWH dalteparin (Fragmin®, Pharmacia, Erlangen, Germany) given as a single bolus injection into the arterial tubing line prior to HD or HDF. The individual dalteparin dosage requirement had been established empirically during several preceding dialysis sessions based on the antiXa levels after 4 h and clinical judgement of the extracorporeal circuit at the end of treatment (no clotting in air traps, clean dialyser/haemofilter). The dalteparin dosage varied considerably between the patients (range 40–96 U/kg).

Blood sampling

For the *in vitro* studies, venous blood was taken from healthy laboratory staff members (aged 22–41 years) or from the dialysis patients. After discarding the first 5 ml, blood was carefully collected from a cubital vein or from the forearm fistula in sterile single-use syringes (B. Braun, Melsungen, Germany) pre-filled with 1/10 Vol dalteparin solution (final calculated dalteparin concentration 0–1.0 antiXa U/ml blood).

For the *in vivo* studies, blood samples were taken immediately before the start of HD treatment and 1, 2, 3 and 4 h thereafter. The first sample (time point 0 h) was drawn from the arterial dialysis needle after clean puncture of the fistula and before application of the anticoagulant. To avoid artificial coagulation activation the first 5 ml of blood were discarded. During extracorporeal circulation blood was collected from the arterial line of the circuit through 20 G steel needles (Terumo, Leuven, Belgium) into sterile syringes and processed without delay.

For the bedside measurement of the whole blood clotting times, native blood was used. To obtain citrated platelet-poor plasma for the other coagulation assays, blood samples were immediately transferred into micro tubes (Sarstedt, Nümbrecht, Germany) containing 1/10 Vol 0.106 M trisodium citrate and kept in ice water (4°C) until further processing. After centrifugation (2000 *g*, 10 min, room temperature) the plasma supernatant was carefully pipetted and stored in small aliquots at –70°C until analysis.

Whole blood clotting times

The whole blood clotting times were carried out as bedside measurements by one experienced laboratory assistant using the ACTester® equipment (Trimed, Huntington Beach, CA, USA). The standard activated clotting time (ACT) was determined according to the manufacturers instructions. Immediately after blood sampling, 500 µl native whole blood was carefully injected in an ACTest blood collection tube (72 x 14, Quest Medical Inc., Allen, TX, USA) containing powdered siliceous earth as activating agent. The tube was inverted three times to allow complete mixing of blood and activator and placed in the ACTester. The clotting time was automatically measured. To determine the normal range, the standard ACT was measured in 16 healthy volunteers (age range 24–41 years).

The factor Xa-ACT was measured essentially as described by Mori *et al.* [18] for the Hemochron device, adapted to the Trimed ACTester. The siliceous earth was completely removed from the test tubes and replaced by 50 µl of a solution containing bovine factor Xa. For the preparation of this solution, the content of one vial of bovine factor Xa (10 IU/vial, F 2027, Sigma Aldrich, Deisenhofen, Germany) was dissolved in 1 ml of sterile isotonic saline. One part of this stock solution was diluted with nine parts isotonic saline giving a factor Xa activity of 1 U/ml. To avoid loss of factor activity, the prepared test tubes and the stock solution were stored for a maximum of 4 weeks in aliquots at –20°C until use. 450 µl of whole blood were injected in the test tube, inverted three times and placed in the ACTester. A final factor Xa activity of 0.1 U/ml as originally proposed by Mori et al. was used.

Other coagulation assays

The antiXa levels were measured in citrated platelet-poor plasma using a chromogenic substrate assay (Coatest LMW Heparin/Heparin®, Chromogenix, Mölndal, Sweden). Commercially available control plasmas with known antiXa activity (0.3 and 0.7 antiXa U/ml) were used for quality control purposes (Chromogenix).

To detect coagulation activation during HD, the thrombin–antithrombin (TAT) complexes were determined with the Enzygost TAT micro® sandwich ELISA (Dade Behring, Marburg, Germany).

Statistical analysis

The statistical calculations were performed using the software package SPSS 10.0 for Windows (SPSS Inc., Chicago, IL, USA). All data are expressed as mean±standard deviation (SD). Bivariate correlation was analysed by calculating the Pearson correlation coefficient.

A linear regression analysis was performed. Violations of the standard assumptions of the linear regression analysis (autocorrelation and heteroscedasticity) could not be found. The Student's *t – l* test for paired or unpaired samples, ANOVA for repeated measurements and univariate ANOVA were employed where appropriate. For multiple comparisons the alpha correction according to Bonferroni was used. Statistical significance was assumed if the two-tailed *P* value was <0.05.

Results

In vitro studies

Using dalteparin-spiked whole blood from five healthy volunteers we compared the effect of increasing amounts of antiXa activity on Xa-ACT and conventional ACT. As shown in Figure 1, both coagulation times showed an increasing prolongation with rising antiXa content of the blood and displayed a strong correlation with the plasma antiXa levels (Pearson correlation coefficients $r = 0.94$ and 0.89, respectively). However, the Xa-ACT revealed a distinctly steeper slope of the correlation curve than the ACT (a = 89.84 *vs* 25.83 s/U) indicating a higher sensitivity for LMWH than the conventional ACT. According to our *in vitro* data the Xa-ACT is able to distinguish between antiXa levels relevant for dialysis patients (0.5–1.0 IU/ml). An antiXa plasma level of 0.6 IU/ml was associated with an Xa-ACT increase from 118±9 (baseline) to 166±9 s (141±5% of baseline). At 1.0 U/ml the Xa-ACT reached 221±16 s (189±22% of baseline), whereas the conventional ACT only increased from 91±8 to 118±11 s (130±12% of baseline). Even a very high antiXa level (2.0 IU/ml) only lead to a moderate prolongation of the conventional ACT (146±11 s, 161±16% of baseline), while in contrast, the Xa-ACT reached 302±27 s (257±28% of baseline).

The Xa-ACT coefficient of variation (CV) was determined by repeated measurement of blood samples spiked with two different dalteparin amounts (0.1 and 0.25 antiXa U/ml whole blood, $n = 5$ each) corresponding to clinically relevant antiXa plasma levels during HD. The CV was found to be 3±0.7 and 2±1%, respectively, indicating an excellent reproducibility of the test.

We also performed an *in vitro* study with dalteparin-spiked blood from five dialysis patients. The correlation curves generated with uraemic blood (regression equations Xa-ACT $y = 99.5x + 127.41$; $r = 0.948$; ACT $y = 30.86x + 103.61$; $r = 0.747$) were similar to the curves obtained with healthy blood indicating that the chronic renal insufficiency itself did not affect the correlation between antiXa levels and the whole blood clotting times.

***In vivo* studies**

The spontaneous Xa-ACT in our dialysis patients was 139±6 s (range 132–150 s, n = 9). The baseline Xa-ACT in the patient group was additionally measured on three consecutive HD sessions before application of the dalteparin bolus. The coefficient of variation was 7±3% indicating a good reproducibility from day to day.

Next, we studied the *in vivo* performance of Xa-ACT and ACT during HD with single bolus dalteparin anticoagulation. Figure 2 displays the overall correlation between Xa-ACT respective to conventional ACT and antiXa levels during dialysis. The Xa-ACT correlated well with the antiXa plasma levels *in vivo* (r = 0.697), however, to a lesser extent than *in vitro* (r = 0.94; see Figure 1). ACT and antiXa level were only weakly correlated (r = 0.522). The calculated change of clotting time per unit change of dalteparin level *in vivo* was 81 s/U for the Xa-ACT and 22 s/U for the ACT.

Table 1 displays the time courses of Xa-ACT, conventional ACT, corresponding antiXa levels and TAT levels (mean±SD) *in vivo* up to 4 h after the dalteparin bolus.

In six patients, receiving a single dalteparin bolus of 80±11 U/kg (range 64–96), the antiXa level after 1 h was 0.94±0.18 IU/ml. The Xa-ACT increased to 170±19% of baseline after 1 h and 160±14% after 2 h. The corresponding conventional ACT values were only 120±10% after 1 h and 115±5% after 2 h. Even 4 h after the bolus injection the Xa-ACT was still significantly elevated (131±17% of baseline). In contrast, the conventional ACT had returned to the baseline level at 3 h (104±8%), although the antiXa level was still in the therapeutic range. In these patients the dalteparin bolus prevented significant TAT complex generation throughout the dialysis session.

In the remaining three patients, who received a distinctly lower dalteparin bolus (40–44 U/kg), we observed a different Xa-ACT respective to ACT time course. The maximum antiXa level 1 h after the bolus was only 0.64±0.11 IU/ml. Correspondingly, the Xa-ACT remained below 200 s after 1 h (125±4% of baseline), but was statistically significantly different from baseline (P = 0.037). The Xa-ACT was back to the baseline levels after 3 h (102±2%) and even fell below the individual baseline values after 4 h (93±7%). In contrast, the conventional ACT did not significantly increase and was only 108±10% of the baseline after 1 h. Similar to the Xa-ACT, the ACT then reached values lower than the baseline. Subsequently, we detected a strong increase of the TAT levels indicating insufficient anticoagulation.

Nevertheless, all HD sessions could be completed without clotting of air traps, tubings or dialysers. Bleeding complications were not observed.

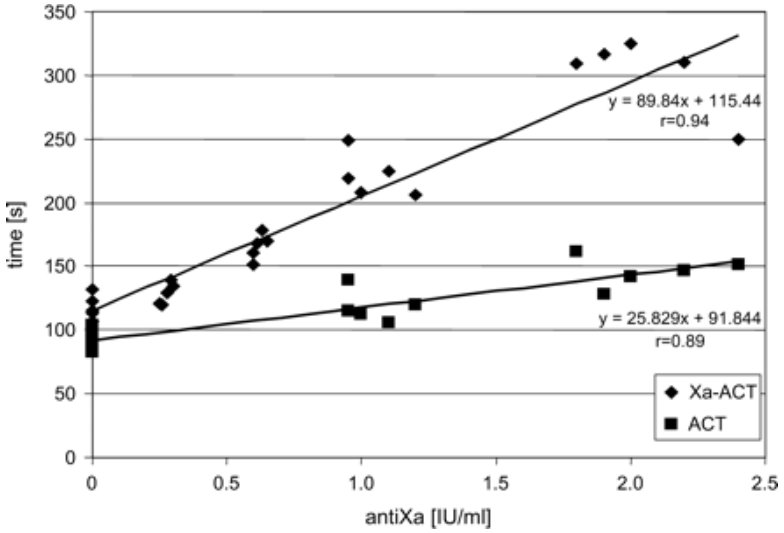


Fig. 1. *In vitro* correlation of Xa-ACT (diamond) and conventional ACT (square) with the plasma antiXa level in dalteparin-spiked blood from healthy volunteers (n = 5). The equations of the correlation curves are given in the diagram.

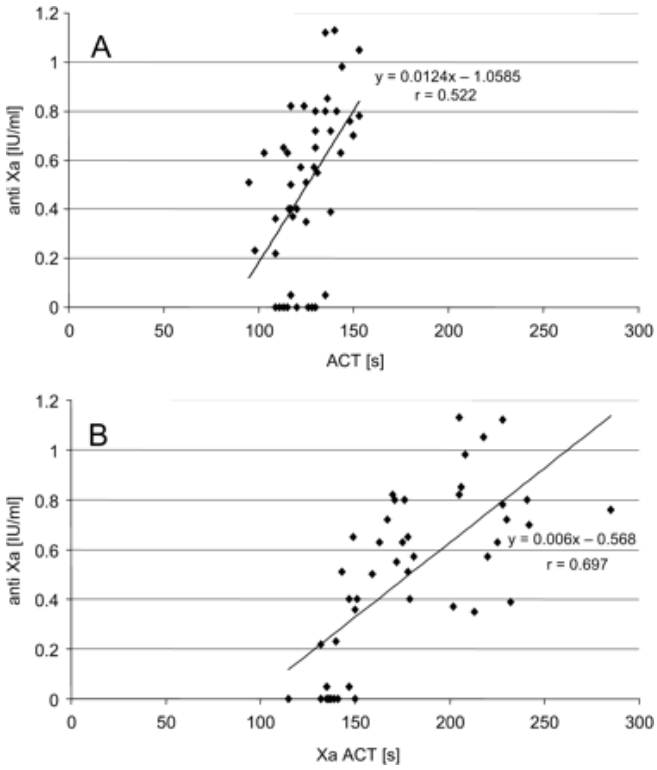


Fig. 2. *In vivo* correlation of (**A**) conventional ACT and (**B**) Xa-ACT with the plasma antiXa level during 4 h of HD treatment. The Pearson correlation coefficient r was 0.522 for ACT and 0.697 for Xa-ACT.

Parameter	*n*	Dalteparin [range]	0 h	1 h	2 h	3 h	4 h
Xa-ACT (s)	6	80±11 U/kg [64–96]	138±5	234±28*	219±15*	191±28*	181±22*
ACT (s)	6		120±9	144±8*	138±10*	125±9	120±11
antiXa (IU/ml)	6		0	0.94±0.18*	0.78±0.12*	0.64±0.16*	0.50±0.15*
TAT (µg/l)	6		3.6±2.1	3.1±1.5	5.1±3.2	5.8±3.1	7.6±2.8
Xa-ACT (s)	3	42±1 U/kg [40–44]	142±6	176±5*	159±16	145±6	131±16
ACT (s)	3		124±8	134±6	116±8	104±14	111±4
antiXa (IU/ml)	3		0	0.64±0.14*	0.51±0.15*	0.38±0.14	0.21±0.20
TAT (µg/l)	3		2.3±0.1	2.4±0.3	5.8±1.6	25.2±15.3	35.0±6.9*

The patients were divided in two subgroups ($n = 6$ and $n = 3$) according to the delivered dalteparin dose. Data are given as mean±SD.

*Indicates $P<0.05$ compared with 0 h (ANOVA).

Table 1. Time courses of Xa-ACT, ACT, antiXa and TAT levels during HD

Discussion

In the present study we evaluated the suitability of the Xa-ACT as a novel tool for the bedside monitoring of LMWH during HD and compared it with the conventional ACT. Our data show that the Xa-ACT is useful for dalteparin monitoring and superior to the conventional ACT.

The Xa-ACT fulfils the criteria of a bedside test, as it is a simple and cheap assay giving a reliable result within minutes. If necessary, the test can be repeated as often as needed during a dialysis session, which is not possible with a chromogenic assay. This modified ACT was described for the first time in 1998 [18], but the published data did not allow drawing final conclusions about the suitability of the method. We therefore decided to study the Xa-ACT during HD with single bolus dalteparin anticoagulation, which has become the standard regimen for LMWH anticoagulated dialysis treatment. Our data substantially extend previous findings.

We could demonstrate that the Xa-ACT correlated well—*in vitro* as well as *in vivo*—with the plasma antiXa activity. The observed correlation coefficient of $r = 0.697$ *in vivo* is comparable with values published for the conventional ACT (r 0.6–0.75) used for the monitoring of UFH in the lower dose range [19–21]. Additionally, the correlation curves obtained for the Xa-ACT showed reasonable slopes, which is an important criterion that has to be taken into account for the judgment of a laboratory method.

The Xa-ACT closely followed the considerably changing antiXa levels. In three patients remarkably high TAT complex levels were detected at the end of the dialysis session indicating insufficient anticoagulation. These patients were distinct from the other six patients in terms of the dalteparin dose received and the peak antiXa levels. This was reflected by the Xa-ACT showing that the Xa-ACT is able to detect insufficiently anticoagulated patients. The *in vitro* data suggest, that the Xa-ACT also has the ability to detect patients with over-anticoagulation. An antiXa level of 2.0 IU/ml was associated with a Xa-ACT of >300 s indicating that exceeding clinically relevant antiXa levels is reflected by the Xa-ACT excluding a so-called 'ceiling effect'.

If the purpose of bedside monitoring of anticoagulation in the clinical practice is defined as the ability to rapidly and reliably stratify the patients as adequately anticoagulated, inadequately too much or too little anticoagulated, thereby preventing bleeding or thrombotic complications, the above described findings suggest that the Xa-ACT is sufficiently accurate and sensitive for the clinical use as LMWH bedside test in dialysis patients. According to the presented data, we would recommend a target Xa-ACT >200 s 1 and 2 h after the LMWH bolus and of >160 s after 4 h in order to suppress coagulation activation. To avoid over-anticoagulation the maximum Xa-ACT should be kept clearly below 300 s. A larger number of patients should be studied to confirm this regimen using Xa-ACT as the primary parameter for dosage adjustments.

There is an ongoing controversy about the role of the conventional ACT in LMWH monitoring. Based on *in vitro* studies suggesting a good correlation between ACT and antiXa concentration, the ACT has been applied to LMWH monitoring [13]. Schulz *et al*. [14] reported positive experiences with the ACT in dalteparin treated dialysis patients and recommended it for monitoring. In a very recent publication, Marmur *et al*. [17] presented *in vitro* and clinical *in vivo* data also supporting the use of the ACT for monitoring dalteparin anticoagulation. In patients undergoing percutaneous coronary interventions they observed a significant increase of the ACT 5 minutes after i.v. administration of 80 U dalteparin/kg body weight from baseline 123±11 to 192±24 s. However, the transferability of their findings to the HD setting is limited: first they achieved this ACT prolongation with an antiXa level (1.9±0.8 IU/ml), which is almost 2-fold higher than the levels typical during HD.

Secondly, the authors did not investigate time points later than 60 min and included patients treated with the glycoprotein IIb/IIIa antagonist abciximab, which has been shown to substantially prolong the ACT [22].

Our data suggest, that the ACT is not a sensitive parameter for LMWH monitoring during HD, although our *in vitro* data showed a strong correlation between antiXa levels and ACT (r = 0.89). However, the low gradient of the correlation curve indicates a poor sensitivity of the ACT compared with the Xa-ACT. Furthermore, although we observed significant ACT changes during the dialysis treatment, the extent of the ACT increase at clinically relevant antiXa levels was comparably small (maximum 20±10% of baseline, corresponding to antiXa 0.94±0.16 IU/ml), which—in our opinion—precludes a reliable monitoring. Our findings are in accordance with a recently published study [15], investigating the conventional ACT during continuous dalteparin infusion. Despite constantly elevated antiXa levels (0.5–0.6 IU/ml) the authors observed a significant increase of the ACT only 10 min after the initial bolus.

In contrast to the chromogenic antiXa activity assay, the Xa-ACT is a functional test, which can be affected by coagulation activation *in vivo* leading to thrombin generation and platelet activation. At a given antiXa level this pre-activation of the blood sample leads to a relatively too short Xa-ACT, thus underestimating the antiXa activity in the blood sample. For the use as a clinical monitoring parameter this should be considered to be an advantage over the chromogenic test, since this feature can be used to detect insufficiently anticoagulated patients by serial measurements as evidenced by our data.

This study focused on the LMWH dalteparin, but other LMWH (e.g. enoxaparin and tinzaparin) are also used for HD. Considering that the LMWH significantly differ regarding molecular weight distribution and pharmacodynamic data [23], the performance of the Xa-ACT could be affected.

Our observations confirm that the dalteparin bolus regimen is safe and effective to prevent coagulation during routine dialysis. A dalteparin bolus of 80±11 U/kg (range 64–96) prevented a significant TAT generation. This is in accordance with the dalteparin dosages used in previously published studies [9–12].

One possible drawback of the Xa-ACT is the need to prepare tubes containing a diluted factor Xa solution and the fact that the factor Xa solution should be stored at temperatures around –20°C to prevent loss of activity. The necessary equipment may not be readily available in every dialysis unit, but this should not a priori invalidate an otherwise useful laboratory method.

In conclusion, our data show that the Xa-ACT is superior to the conventional ACT for the bedside monitoring of LMWH anticoagulation during HD treatment, suggesting that the Xa-ACT can serve as a LMWH monitoring parameter for the clinical practice. This should be proven in a larger clinical study with Xa-ACT as the primary monitoring tool. The conventional ACT was much less sensitive to LMWH than the Xa-ACT and did not prove suitable for LMWH monitoring.

References

1. Kraatz G, Lopot F. Messung der aktivierten Vollblutgerinnung als Kontrollparameter für die Heparindosierung bei Hämodialyse. *Z Urol Nephrol* 1984; 77: 465–471[Medline]

2. Stenbjerg S, Berg E, Albrechtsen OK. Evaluation of the activated whole blood clotting time (ACT) *in vitro*. *Scand J Haematol* 1979; 23: 239–244[Medline]

3. Lord H, Jean N, Dumont M, Kassis J, Leblanc M. Comparison between tinzaparin and standard heparin for chronic hemodialysis in a Canadian center. *Am J Nephrol* 2002; 22: 58–66[CrossRef][Medline]

4. Borm JJJ, Krediet R, Sturk A, ten Cate JW. Heparin versus low molecular weight heparin K 2165 in chronic hemodialysis patients: a randomized cross-over study. *Haemostasis* 1986; 16 [Suppl. 2]: 59–68

5. Deuber HJ, Schulz W. Reduced lipid concentrations during four years of dialysis with low molecular weight heparin. *Kidney Int* 1991; 40: 496–500[Medline]

6. Schmitt Y and Schneider H. Low-molecular-weight heparin (LMWH): influence on blood lipids in patients on chronic haemodialysis. *Nephrol Dial Transplant* 1993; 8: 438–442[Abstract/Free Full Text]

7. Warkentin TE, Levine MN, Hirsh J *et al*. Heparin-induced thrombocytopenia in patients treated with low molecular-weight heparin or unfractionated heparin. *N Engl J Med* 1995; 332: 1330–1335[Abstract/Free Full Text]

8. Schrader J, Stibbe W, Armstrong VW *et al*. Comparison of low molecular weight heparin to standard heparin in hemodialysis/hemofiltration. *Kidney Int* 1988; 33: 890–896[Medline]

9. Baumann D, Frühsorger A, Glass W, Zielke E. Bolusapplikation von Fragmin zur Antikoagulation in der Hämodialyse. *Nieren- u Hochdruckkrankheiten* 1991; 20: 36–40

10. Ljungberg B, Blombäck M, Johnsson H, Lins LE. A single dose of a low molecular weight heparin fragment for anticoagulation during hemodialysis. *Clin Nephrol* 1986; 27: 31–35

11. Hafner G, Swars H, Ehrenthal W, Schinzel H, Weilemann LS, Prellwitz W. The control of anti-coagulation in acute dialyses with sensitive laboratory parameters. *Scand J Clin Lab Invest* 1992; 52: 289–296[Medline]

12. Sagedal S, Hartmann A, Sundstrom K, Bjornsen S, Fauchald P, Brosstad F. A single dose of dalteparin effectively prevents clotting during haemodialysis. *Nephrol Dial Transplant* 1999; 14: 1943–1947[Abstract/Free Full Text]

13. Briel RC, Zielke E, Zwirner M. Untersuchungen zur Korrelation der anti-Faktor Xa-Aktivität von niedermolekularem Heparin (Fragmin) und der aktivierten Vollblutgerinnungszeit im AC-Tester. *Ärztl Lab* 1987; 33: 237–240

14. Schulz W, Deuber HJ, Günthner R, Ohrisch G, Eichhorn M, Werthmann G. Aktueller sand des einsatzes von niedermolekularem heparin in der hämodialyse-therapie. *Nieren- u Hochdruckkrankheiten* 1995; 24: 187–197

15. Greiber S, Weber U, Galle J, Brämer P, Schollmeyer P. Activated clotting time is not a sensitive parameter to monitor anticoagulation with low molecular weight heparin in hemodialysis. *Nephron* 1997; 76: 15–19[ISI][Medline]

16. Henry TD, Satran D, Knox LL, Iacarella CL, Laxson DD, Antman EM. Are activated clotting times helpful in the management of anticoagulation with subcutaneous low molecular weight heparin? *Am Heart J* 2001; 142: 590–593[CrossRef][ISI][Medline]

17. Marmur JD, Anand SX, Bagga RS, Fareed J, Pan CM, Sharma SK, Richard MF. The activated clotting time can be used to monitor the low molecular weight heparin dalteparin after intravenous administration. *J Am Coll Cardiol* 2003; 41: 394–402[Abstract/Free Full Text]

18. Mori M, Yoshitake S, Kitano T, Oda S, Noguchi T. Measurement of whole blood factor Xa-activated clotting time during hemodialysis with low-molecular-weight heparin. *J Anesth* 1998; 12: 130–132

19. Koerber JM, Smythe MA, Begle RL, Mattson JC, Kershaw BP, Westley SJ. Correlation of activated clotting time and activated partial thromboplastin time to plasma heparin concentration. *Pharmacotherapy* 1999; 19: 922–931[CrossRef][ISI][Medline]

20. Smythe A, Koerber JM, Nowak SN, Mattson JC, Begle RL, Westley SJ, Balasubramaniam M. Correlation between activated clotting time and activated partial thromboplastin times. *Ann Pharmacother* 2002; 36: 7–11

21. Bommer J, Schwab M. Bedside testing with the new CoaguChek Pro activated clotting time assay in dialysis. *Artif Organs* 2002; 26: 387–90[Medline]

22. Ambrose JA, Hawkey M, Badimon JJ *et al*. *In vivo* demonstration of an antithrombin effect of abciximab. *Am J Cardiol* 2000; 86: 150–152[CrossRef][ISI][Medline]

23. Samama MM, Gerotziafas GT. Comparative pharmacokinetics of LMWHs. *Semin Thromb Hemost* 2000; 26 [Suppl. 1]: 31–38

Received for publication: 6. 8.03
Accepted in revised form: 9. 2.04

[Acknowledgements omitted.]

A final basic-article discusses the basic pharmacology of the heparin-family of drugs:

http://scv.sagepub.com/cgi/content/abstract/7/4/357

Seminars in Cardiothoracic and Vascular Anesthesia, Vol. 7, No. 4, 357-377 (2003)

Unfractionated and Low-Molecular-Weight Heparins, Basic Mechanism of Action and Pharmacology

Jawed Fareed, PhD

Departments of Pathology and Pharmacology, Hemostasis and Thrombosis Research Laboratories, Loyola University Chicago, 2160 South First Avenue, Maywood, IL 60153; jfareed@lumc.edu

Qing Ma, PhD

Michelle Florian, BS

Jyothi Maddineni, MS

Omer Iqbal, MD

Debra A. Hoppensteadt, PhD

Departments of Pathology and Pharmacology, Loyola University Chicago,

Rodger Bick, MD

Departments of Medicine and Pathology, University of Texas Southwestern Medical Center, Dallas, Texas

> Unfractionated heparin has enjoyed sole anticoagulant status for nearly 50 years. Despite a dramatic growth in the development and the introduction of many newer anticoagulant and antithrombotic drugs and polytherapeutic approaches during the past decade, unfractionated and low-molecular-weight heparins remain the drugs of choice for many indications, including surgical anticoagulation, interventional cardiology, and in several additional considerations.
>
> Unfractionated heparin has a major role in the areas of vascular medicine and surgery, and it is the only parenteral anticoagulant drug that can be empirically neutralized by such agents as protamine sulfate.
>
> The development of low and ultra low-molecular-weight heparins, which are a class of depolymerized heparin derivatives with distinct pharmacologic profiles that are largely determined by their composition, represents a refinement for the use of heparin. These drugs produce their major effects by combining with antithrombin Ill and exerting antithrombin and anti-Xa inhibition. The low-molecular-weight heparins also increase non-antithrombin III-dependent effects, such as tissue factor pathway inhibitor release, modulation of adhesion molecules, and the release of profibrinolytic and antithrombotic mediators from the blood vessels.
>
> Each of the low-molecular-weight heparins has different cumulative effects, and each product exhibits a distinct profile. Initially developed for the prophylaxis of postsurgical deep vein thrombosis, these drugs are now also used for the treatment of both venous and arterial thrombotic disorders. To a large extent, the low-molecular-weight heparins have replaced unfractionated heparin in most of the subcutaneous indications.
>
> This has resulted in a dramatic evolution in anticoagulant management that allows patients with thrombotic disorders to be treated in an outpatient setting. Thus, the introduction of low-molecular-weight heparins represents a major advance in improving the use of heparin. Generic versions of these drugs are likely to be developed as their patents expire.
>
> Currently, there are no clear guidelines for the acceptance of the generic versions of branded products. To avoid safety and efficacy-related problems, a generic drug must meet both the chemical and biologic equivalence criterion. Synthetically and biosynthetically derived agents such, as pentasaccharide, will also be introduced for clinical use; however, these drugs will have a narrower therapeutic spectrum due to their monotherapeutic nature. Heparin and its derivatives will continue to have a crucial role in the management of thrombotic and cardiovascular disorders in years to come.

These three articles *seriatim* show that Lovenox monitoring was available and validated; that the Xa-ACT is superior to the conventional ACT for the bedside monitoring of LMWH anticoagulation; and that Lovenox affects AT-III, Xa, and other molecules.

Previously, prescribing information provided by Aventis was cited [page 35, *et seq*.]. Because of the need to compare/contrast the depiction of the database with its contents, the current provision of information/conclusions to the public (and physicians) is cited:

http://products.sanofi-aventis.us/lovenox/lovenox.html#8.1

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure. The fetal risk summary below describes the potential of Lovenox to increase the risk of developmental abnormalities above background risk.

Fetal Risk Summary

Lovenox is not predicted to increase the risk of developmental abnormalities. Lovenox does not cross the placenta, based on human and animal studies, and shows no evidence of teratogenic effects or fetotoxicity.

Cases of "Gasping Syndrome" have occurred in premature infants when large amounts of benzyl alcohol have been administered (99-405 mg/kg/day). The multiple-dose vial of Lovenox contains 15 mg benzyl alcohol per 1 mL as a preservative [see *Warnings and Precautions (5.8)*].

Clinical Considerations

It is not known if either dose adjustment or monitoring of anti-Xa activity of enoxaparin are [sic; should be "is"] necessary during pregnancy.

Pregnancy alone confers an increased risk for thromboembolism that is even higher for women with thromboembolic disease and certain high risk pregnancy conditions. While not adequately studied, pregnant women with mechanical prosthetic heart valves may be at even higher risk for thrombosis [see *Warnings and Precautions (5.7) and Use in Specific Populations (8.6)*]. Pregnant women with thromboembolic disease, including those with mechanical prosthetic heart valves and those with inherited or acquired thrombophilias, have an increased risk of other maternal complications and fetal loss regardless of the type of anticoagulant used.

All patients receiving anticoagulants such as enoxaparin, including pregnant women, are at risk for bleeding. Pregnant women receiving enoxaparin should be carefully monitored for evidence of bleeding or excessive anticoagulation. Consideration for use of a shorter acting anticoagulant should be specifically addressed as delivery approaches [see *Boxed Warning*]. Hemorrhage can occur at any site and may lead to death of mother and/or fetus. Pregnant women should be apprised of the potential hazard to the fetus and the mother if enoxaparin is administered during pregnancy.

Data

Human Data - There are no adequate and well-controlled studies in pregnant women.

A retrospective study reviewed the records of 604 women who used enoxaparin during pregnancy. A total of 624 pregnancies resulted in 693 live births. There were 72 hemorrhagic events (11 serious) in 63 women. There were 14 cases of neonatal hemorrhage. Major congenital anomalies in live births occurred at rates (2.5%) similar to background rates.

There have been postmarketing reports of fetal death when pregnant women received Lovenox. Causality for these cases has not been determined. Insufficient data, the underlying disease, and the possibility of inadequate anticoagulation complicate the evaluation of these cases.

A clinical study using enoxaparin in pregnant women with mechanical prosthetic heart valves has been conducted [see *Warnings and Precautions (5.7)*].

Animal Data - Teratology studies have been conducted in pregnant rats and rabbits at SC doses of enoxaparin up to 30 mg/kg/day or 211 mg/m^2/day and 410 mg/m^2/day, respectively. There was no evidence of teratogenic effects or fetotoxicity due to enoxaparin. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

This case is now assessed *de novo*, based on the extensive database summarized herein. The result is that information contained in the Aventis coffers was apparently suppressed.

The direct result of the dissemination of such information would have been that Dr. Khan would have either chosen another agent or employed a monitoring test (if dosages would be affected by the assessment of additional information regarding its effects); either way, potential toxicity to mother/fetus would have been precluded and/or ameliorated. Also, as discussed *supra*, it is clear that the permanent effects upon the baby (Savannah)—intracranial hemorrhage causing global developmental delays, cerebral palsy, seizures, auditory processing disorders, deafness, and blindness—have stressed-out the patient.

It is now necessary to compile the data that were acquired from Aventis regarding the potential that adverse reactions occurred following the use of Lovenox. Noting that the data are extensive, review of these reports (excerpted prior to receipt by this physician) necessarily is limited to what others (who have reviewed all binders, over the years) determined to have potential import. Therefore, the indexing system that has been used herein is tethered to the raw data, with potential implications distilled independently.

It is also necessary to compile the outcome of serial decision-making activity by Aventis regarding how these data were to be processed internally and then portrayed externally. Here, it is mandatory that whatever may have transpired be "processed" in a fashion that is both disinterested (based on reported information, not withstanding what might have been requested to clarify sparsely-documented clinical events) and comprehensive. Thus, this initial outline is drawn directly from the "Full ADR Index" for Binders 8-12.

6/23/1993 – 12/30/1993

1. Cranial Bleed Episode.
   {MASTER BINDER 8:ADR 1, Section A1}

2. Duplicate Provided.
   {8:1,A2}

3. Contains history of and statistics of enoxaparin usage and additional adverse reaction reports

   Spontaneously Reported Cases of Thrombocytopenia Associated with Enoxaparine Administration [AVE 008513]
   Patient Index Summary [AVE 008519]
   Additional ADRs [AVE 008529]
   FETAL DEATH incident [AVE 008530]
   {8:1,A3}

1/12/1994 – 5/27/1994

4. ADR [AVE 008536]
   ADR – FETAL DEATH [AVE 008540]
   FDA Periodic Report Extract [AVE 011939]
   {8:1,B}

6/8/1994 – 8/11/1994

5. --
   {8:1,C}

1/5/1996 – 5/28/1996

6. --
{8:1,D}

5/30/1997

7. ADRs (Adverse Reaction Reports) from Rhone-Poulenc Rorer Pharm.
{8:1,E1}

8. ADR summary
{8:1,E2}

6/2/1997 – 9/30/1997

9. Fetal Death
{9:2,A}

5/28/1998

10. Summary of ADRs:
Contains Index of FDA 3500's which includes Manuf. Rpt Number and Adverse Event Synonym Mar. 29, 1997 - Mar. 28, 1998
{9:2,B}

11. Fetal Incident
{9:2,C}

May 28, 1999

12. ADR Summary
Contains Index of FDA 3500's which includes Manuf. Rpt Number and Adverse Event Synonym: March 29, 1998 to March 28, 1999
{9:2,D}

October 4, 1999 – December 29, 1999

13. ADR Fetal distress - High dosage of enoxaparin
{9:2,E}

Jan. 4, 2000 to Mar. 31, 2000

14. Pregnancy Incident [AVE 009028]
ADR Death of Mother- Investigator considered event related to study drug.
{9:2,F}

April 3, 2000 – May 31, 2000

15. Pregnancy Studies ADR [AVE 009039]
A study with Adverse Reaction events reported
{9:2,G}

16. Listing of 15-day Alerts Submissions. **Note: Page 23 of 23 (of listing document) is Missing** – should follow AVE 009077
Contains Narrative summary of adverse drug "experiences" for the period 29-Mar-1999 to 28-Mar-2000.
Listing of Alert Submissions [AVE 009056]
Narrative Summary [AVE 009078]
Distribution of ADR by Body System [AVE 009132]
Narrative of Action Taken [AVE 009152]
{9:2,H}

August 1, 2000 – Nov. 28, 2000

17. ADRs - Draft of Article written with concern over exonaparine
Anaphylactic Shock associated with Enoxaparin (Lovenox) Therapy: A Report of Three Cases, Review of the Literature and Discussion
Author: REDACTED [AVE 009160]
{9:2,I}

December 1, 2000 to February 28, 2001

18. ADRs
{9:2,J}

March 7, 2001 to May 30, 2001

19. ADRs
{9:2,L}

June 11, 2001

20. ADRs
{9:2,M}

21. ADRs
{10:3,A}

22. ADRs
{10:3,B1}

23. Table 1: Serious and Unexpected Events, March 29, 2000 to March 28, 2001
{10:3,B2}

24. Table 2: Serious and Expected Events, March 29, 2000 to March 28, 2001
(10:3,B3}

25. Index, Table 3: Non-Serious Domestic Spontaneous Events, March 29, 2000 to March 28, 2001
{10:3,B4}

26. Index, Table 4: SU Events by System Organ Class, March 29, 2000 to March 28, 2001
{10:3,B5}

27. Index, Table 5: SE, NE, & NU Events by System Organ Class, March 29, 2000 to March 28, 2001
{10:3,B6}

28. Index, Table 6: Events Resulting in Death, March 29, 2000 to March 28, 2001
{10:3,B7}

29. Listing of 15-day Alerts Submitted, March 29, 2000 to March 28, 2001
{10:3,B8}

30. Index of FDA 3500's March 29, 2000 to March 28, 2001
{10:3,B9}

31. Narrative Summary [AVE 009982]
Insert Rev. 1/2000 [AVE 009984]
{10:3,B10}

June 1, 2001 to August 30, 2001

32. Selected ADLs
{11:4,A}

Sept. 5, 2001 to Dec. 28, 2001

33. Selected ADRs – Pregnancy, fetal death related
{11:4,B}

Jan. 2, 2002 to May 2, 2002

34. Pregnancy related ADR [AVE 010020]
Pregnancy related ADR [AVE 010022]

Case Report: Massive choroidal hemorrhage associated with LMW heparin therapy
Author: M. Neudorfer
Source: Blood Coagulation and Fibrinolysis 2002, 13: 257 – 259
[AVE 010033]

Pregnancy related ADR [AVE 010038]
Pregnancy related ADR [AVE 010044]
Pregnancy related ADR [AVE 010048]
Pregnancy related ADR [AVE 010050]
{11:4,C}

May 23, 2002

35. –
{11:4,D}

June 11, 2002 to July 30, 2002

36. Pregnancy related ADR [AVE 010070]
Pregnancy related ADR [AVE 010072]
Fetal Death ADR [AVE 010077]
{11:4,E}

Aug. 2, 2002 to Dec. 30, 2002

37. Pregnancy related ADR [AVE 010085]
Pregnancy related ADR [AVE 010087]
Pregnancy related ADR [AVE 010089]
Pregnancy related ADR [AVE 010091]
Pregnancy related ADR [AVE 010093]
Pregnancy related ADR [AVE 010095]
Fetal related ADR [AVE 010097]
Fetal related ADR [AVE 010100]
Pregnancy related ADR [AVE 010104]
{11:4,F}

January 3, 2003 to May 28, 2003

38.	Pregnancy related ADR	[AVE 010107]
	Pregnancy related ADR	[AVE 010109]
	Pregnancy related ADR	[AVE 010112]
	Fetal death ADR	[AVE 010114]
	Pregnancy related ADR	[AVE 010116]
	Pregnancy related ADR	[AVE 010118]
	Pregnancy related ADR	[AVE 010120]
	{11:4,G}	

May 29, 2003 to Sept. 29, 2003

39.	Pregnancy related ADR	[AVE 010123]
	Pregnancy related ADR	[AVE 010125]
	Pregnancy related ADR	[AVE 010129]
	Fetal related ADR	[AVE 010131]
	Pregnancy related ADR	[AVE 010133]
	Fetal related ADR	[AVE 010135]
	Pregnancy related ADR	[AVE 010137]
	Pregnancy related ADR	[AVE 010140]
	Pregnancy related ADR	[AVE 010142]
	Fetal related ADR	[AVE 010144]
	Pregnancy related ADR	[AVE 010147]
	{11:4,H}	

October 1, 2003 to December 31, 2003

40.	Fetal Death ADR	[AVE 010150]
	Pregnancy related ADR	[AVE 010153]
	Fetal related ADR	[AVE 010155]
	Pregnancy related ADR	[AVE 010157]
	Pregnancy related ADR	[AVE 010159]
	Pregnancy related ADR	[AVE 010161]
	Fetal death ADR	[AVE 010164]
	Fetal related ADR	[AVE 010166]
	Pregnancy related ADR	[AVE 010174]
	Pregnancy related ADR	[AVE 010176]

Article: **Use of low molecular mass heparin (enoxaparin) in newborn infants: a prospective cohort study of 62 patients [**Author: REDACTED]
Source: Arch Dis Child Fetal Neonatol Ed 2003; 88: F365 – F370
[AVE 010168]
{11:4,I}

[Internal] Contents

This tabulation is provided to facilitate identifying information that is to be distilled. The number to the left refers to the above listing of each group of referenced items, and the number to the right refers to the initial page # at which elaborative information exists.

There are additional reports extended for another few years but, inasmuch as this case relates to events that transpired prior to a 2003-delivery, distillation thereof is deferred. Thus, the next step is to fact-check the summary points gleaned from the Master Binders by reviewing each file therein, and then contrasting/amending the contents thereof with what has been distilled *supra*. No effort is yet made to "process" these raw data, yet, except to the degree to which files have been selected for inclusion herein. Particularly with regard to the early case reports, there was a potential tendency to capture any issue that might possibly lead to a greater understanding of the potential this new agent might have to cause unexplained toxicity. Here, instead, knowing the key-facets of a case that relates to a cerebral hemorrhage in a newborn following a high-risk pregnancy, it is not inappropriate to focus on a subcategory of cases. This did not constitute an inappropriate "retroactive study of a patient subpopulation" because the nature of this type of review necessitated that drug labeling remained accurate (a concept to be referenced *infra*). {The first Word Document in each of the five Binders is identical to the distillations; also, although it would be easier simply to cut/paste these PDF-documents, this would consume a lot of pixels and would make it more difficult to disseminate this letter electronically and, therefore, the provision of the page numbers provided on each sub-file ("AVE xxxxxx") will suffice for the purpose of linking to any potential additional data.}
It is also problematic that the information provided is possibly incomplete, inasmuch as the forms were apparently provided as double-sided submissions with only one side being copied for review; entry #7 (particularly crucial because this is the site for clinical data) being particularly apt to be "continued" on a page that was not available for review.

6/23/1993 – 12/30/1993

1. Cranial Bleed Episode.
{MASTER BINDER 8:ADR 1, Section A1}

To provide a sense of what has appropriately been noted and excluded by whomever prepared the binder-distillation, a few additional entries are now to be briefly digested. This will also provide an example of how pages are being referenced in this letter. Rather than recount the disclaimers in the submitted documents, it is assumed that the patients have all received Lovenox; dependence on the submitted précis is also noted.
Some cases represent follow-up reports but, because the basic issues are tangential, efforts to correlate same have been deferred. This compilation of "pertinent negatives" thereby serves to illustrate what subsequently has been silently noted in these files.

On some level, particularly when a patient had only been transiently using this agent, assuming there was any relationship between its presence and the clinical event may be grossly inappropriate. This is a hurdle that must be superseded when the ultimate review of these data is generated, prior to concluding Aventis ever "misbehaved" in any fashion. Bleeding from excessive dosage and clotting from insufficient dosage might appear to be a "gimme," but detectable trends must be identified to ensure proper guidance has been given to subsequent prescribers (as well as to the FDA and to potential patients). Here, the one case that was identified in the initial listing has been **highlighted** and all data have been dutifully copied. Otherwise, diagnoses have been preserved "telegraphically."

AVE008472 depicts a patient who had pulmonary emboli.

AVE008475 depicts a patient who developed leucopenia.

AVE008478 depicts a patient who had an ischemic cerebrovascular accident ["CVA"].

AVE008481 depicts a patient who had excessive blood-loss.

AVE008484 depicts a 60 year-old woman who died in the post-op setting (knee surgery) from heparin-induced thrombocytopenia ["HIT"], after a cerebral hemorrhage. It is noted that the clinical summary has potentially-contradictory information, but the thrust of the case seems to be that the patient developed this complication promptly after the drug had been initiated (not withstanding performance of a non-essential cholecystectomy). Here, the drug had been given for nine days (inclusive) before the CVA presented, and it was given for an additional two days before HIT was suspected (and, presumably, the drug was then stopped). There is no citation of concomitant Coumadin, although the labs suggest that the predominant effect was on platelets (10K nadir) and not PT/aPTT.

Assessment: Ultimately, because dosage-related information has not been provided, determining the cause of the HIT (for example, whether it was idiosyncratic vs. whether the risk thereof was enhanced by some unreported factor) cannot be definitively ID'ed.

AVE008491 depicts a patient who was given Lovenox despite a history of HIT.

AVE008494 depicts a patient who had a PE three days after having stopped Lovenox.

AVE008498 depicts a patient who had a CVA (presumably associated with hypertension and subsequently-imaged normal pressure hydrocephalus) ten hours after Lovenox.

AVE008502 depicts a patient who had a GI-bleed (and subsequent PE) while on both Lovenox/Coumadin; dosage/chronology data are not included in this submission.

AVE008506 depicts a woman who developed DVT during her third month of pregnancy; it started in the sural vein and extended into the iliac vein before causing a PE. Thus, she was given unfractionated heparin for a month, daleparin for a month, and then Lovenox (40 mg daily during months #5-7 and 20 mg daily during month #8). Finally, "At week #37 (after last menstrual period date), placental detachment was observed with hemorrhage, needing delivery by Caesarian Section. Death *in utero*. No maternal complication." [This report was provided through a French drug subsidiary.]

Assessment: ***This case provides a precise model for what transpired in the instant case, even featuring the dosage-decrement and the potential for transplacental transmission.***

2. Duplicate Provided [Aventis-authored clinical information, grist for comparison]. {8:1,A2}

3. Contains history of and statistics of enoxaparin usage and additional adverse reaction reports

Spontaneously Reported Cases of Thrombocytopenia Associated with Enoxaparine Administration [AVE 008513]
Patient Index Summary [AVE 008519]
Additional ADRs [AVE 008529]
FETAL DEATH incident [AVE 008530]
{8:1,A3}

These relate to a HIT-pathogenesis, noting that 6/17 patients had confirmatory lab studies (while the others lacked a DIC-component) and 4/5 of the references related to HIT (while the first was an internal New Drug Application citation). Six patients died, two with intracerebral hemorrhage from severe thrombocytopenia (71 and 90 years of age). Regarding the fraternal twins, data were not reported (on the appended table) related to three criteria (prior use of either heparin or LMWH, prior thrombocytopenia, lab testing):

SUMMARY OF CASES REPORTED

Since enoxaparin was first marketed in October, 1987, 60 cases of thrombocytopenia defined as platelet counts below 75.000/mm^3 have been reported to the Rhône-Poulenc Rorer Worldwide Pharmacovigilance Department. Fifty-seven cases were reported in France and two cases were reported in Germany. Each of these cases are summarized in the appended tables and CIOMS forms. One case of thrombocytopenia has been reported in the United States, since enoxaparin's launch in May, 1993. This case is discussed separately. The cut off date for this summary is June 30, 1993.

One case of fraternal twins born with neonatal thrombocytopenia was reported. The female twin's platelet count was 20,000/mm^3 at birth and normalized by day 4 of life. The male twin's actual platelet count was not reported. The twin's mother received enoxaparin 40 mg daily during the last five weeks of her pregnancy for venous thromboembolism prophylaxis. She did not herself develop thrombocytopenia.

In summary, sixty spontaneously reported cases of thrombocytopenia in enoxaparin treated patients which include nine cases of thrombosis, three cases of fatal intracranial hemorrhage and two cases of neonatal thrombocytopenia are consistent with the event rates and types of events that might be expected to be observed with this pharmaceutical class, anticoagulants derived from unfractionated heparin. Through December 31, 1992, 47.5 million doses of enoxaparin in the 20 mg formulation form and 53.4 million doses of enoxaparin in the 40 mg formulation have been sold. Assuming that the average enoxaparin treated patient received one dose of either formulation daily for ten (10) consecutive days, an estimate of 10.1 million patient exposures is obtained. Given this estimated number of exposures to drug, a total of 60 reported cases of thrombocytopenia does not reflect an excess occurrence of this event in the treated patient population. The only predictive and effective monitoring procedure for these patients is the periodic performance of platelet counts during the first therapy. Platelet counts should be performed every two to three days during the first two weeks of therapy; declines in platelet count below 100,000/mm^3 or more than 40% below base line count, even if the total platelet count remains above 100,000/mm^3, should be considered as predictive of the imminent onset of thrombocytopenia or thrombosis related to enoxaparin (4, 5).

Assessment: Not withstanding the rationalization that this is an uncommon occurrence, this documents the fact that at least once instance of a transplacental event transpired.

AVE 008530 depicts a "Fetal Death" incident involving a 35 year-old woman who had previously been heparinized during her first pregnancy (with a normal outcome thereof).

SIX MONTHS WAS NORMAL AND PATIENT WAS PLACED ON ENOXAPARIN DUE TO A SUSPECTED KNEE PHLEBITIS. REPORT INDICATES ANTI-XA WAS 0.95 THREE DAYS AFTER THERAPY INITIATION. FETAL DEATH WAS DISCOVERED WHEN PATIENT PRESENTED TO THE "MATERNITY" DUE TO CONTRACTIONS AND AN ECHOGRAPHY WAS PERFORMED. FETAL AUTOPSY REVEALED BILATERAL HEMOTHORAX. DATE OF EVENT IS QUESTIONABLE. RPR PHARMACOVIGILANCE HAS DETERMINED EVENT TO BE REASONABLY ASSOCIATED WITH THE USE OF ENOXAPARIN. (CARES #: PK S 01695.) FURTHER INFORMATION REQUESTED.
F/U 22-OCT-93: RPR FRANCE STATES ANTI-XA WAS "WITHIN THE RANGE SEEN IN THE TREATMENT". CONFIRMS PHLEBITIS WAS SUSPECTED.
F/U 25-OCT-93: RPR FRANCE REPORTS FETAL MOVEMENTS STOPPED THREE DAYS BEFORE ECHOGRAPHY REVEALED FETAL DEATH. CONFIRMS BILATERAL HEMOTHORAX BY AUTOPSY WITH NO APPARENT MALFORMATION.
F/U 16-NOV-93: RPR FRANCE PROVIDES THE FOLLOWING AUTOPSY SUMMARY -
-FETAL DEATH IN UTERO OF A 28-WEEK MALE FETUS WITH ORGAN LYSIS.
-ABSENCE OF ALL FETAL MALFORMATION AND NO GROWTH RETARDATION.
-HYPOTROPHIC PLACENTA WITH THE PRESENCE OF INFARCTED AREAS OF VARYING AGE (BUT NOT RECENT). DUE TO THE LACK OF FETAL HYPOTROPHY, IT IS DIFFICULT TO CONSIDER A PLAUSIBLE RELATION BETWEEN THE FETAL DEATH AND THESE INFARCTS.
-NO SIGNS OF INFECTION (OF THE FETUS) AND NO INFLAMMATION OF THE UMBILICAL CORD.
-THE PRESENCE OF BILATERAL HEMORRHAGIC PLEURAL EFFUSION AND INHALATION OF HEMORRHAGIC AMNIOTIC FLUID SEEMS TO BE THE CAUSE OF FETAL DEATH.
FURTHER INFORMATION EXPECTED.
F/U 07-DEC-93: RPR FRANCE PROVIDES ADDITIONAL INFORMATION PRIMARILY RELATED TO DEMOGRAPHIC DETAILS.

Assessment: There is a dearth of specific data regarding the chronology of anti-Xa tests; apparently, only one (normal) value was acquired, early in the patient's six-day course. Because the fetus had experienced intrathoracic hemorrhage, the conclusion was justified that there was linkage; that the hypotrophic placenta had shown infarcts (of varying age) provides an additional clue to a possible pathogenesis of what had suddenly transpired.

1/12/1994 – 5/27/1994

4.	ADR	[AVE 008536]
	ADR – FETAL DEATH	[AVE 008540]
	FDA Periodic Report Extract {8:1,B}	[AVE 011939]

AVE 008536 depicts an episode of agranulocytosis.

[AVE 008540 depicts the identical fetal death as that detailed under AVE 008530.]

[AVE 011939 also depicts the aforementioned fetal death, included within a table.]

6/8/1994 – 8/11/1994

5. -- [Aventis-authored clinical information, grist for comparison].
{8:1,C}

1/5/1996 – 5/28/1996

6. -- [Aventis-authored clinical information, grist for comparison].
{8:1,D}

5/30/1997

7. ADRs (Adverse Reaction Reports) from Rhone-Poulenc Rorer Pharm.
{8:1,E1}

AVE008551 depicts Anemia and elevated aPTT experienced following Lovenox.

8. ADR summary
{8:1,E2}

AVE008968 depicts a tabular listing of aforementioned ADRs, including "fetal death"; because the aforementioned case does not fall within this time-frame [3/29/96 – 3/28/97], it cannot be assumed that Manufacturer Control Number 01-011211 cites this entry.

Assessment: The information related to MCN 01-011211 needs to be reviewed.

6/2/1997 – 9/30/1997

9. Fetal Death
{9:2,A}

AVE008974 depicts what appears to have been a spontaneous abortion of a 2# fetus @ 36 weeks' gestation (upon which there was an unremarkable autopsy) of a 22 year-old woman who had been taking Lovenox for an unknown period at an unknown dosage.

Assessment: There is insufficient information upon which to base a definitive judgment but, in light of the fact that the fetus demonstrated no hemorrhage, it is possible to be suggestive that there was no relationship between this agent and what later transpired. For example, there is no information regarding whether there was any placental anomaly.

AVE008977 depicts a 33 year-old prime-ip who experienced pyelonephritis-induced sepsic-shock/DIC at the end of the third trimester; six months hence, because ultrasound showed hydrocephalus, there was a therapeutic abortion. Autopsy showed hemorrhage, but it is likely this was due to the acute coagulopathy rather than due to the Lovenox.

Assessment: There is insufficient information upon which to base a definitive judgment but, in light of the fact that the fetus demonstrated hemorrhage, it is not possible to be conclusive that there was no relationship between this agent and what later transpired. For example, there is no information regarding whether there was any placental anomaly, and it is therefore possible that the subsequent findings were caused by the Lovenox.

AVE008981 depicts a series of medical events unrelated to the use of Lovenox.

5/28/1998

10. Summary of ADRs:
Contains Index of FDA 3500's which includes Manuf. Rpt Number and Adverse Event Synonym Mar. 29, 1997 - Mar. 28, 1998
{9:2,B}

AVE008986 lists the major diagnoses for ADRs in tabular form; none is germane.

11. Fetal Incident
{9:2,C}

AVE009003 depicts a woman who had fetal distress, but no adverse sequellae.

May 28, 1999

12. ADR Summary
Contains Index of FDA 3500's which includes Manuf. Rpt Number and Adverse Event Synonym: March 29, 1998 to March 28, 1999
{9:2,D}

AVE009001 lists the major diagnoses for ADRs in tabular form; US01-19841 was a miscarriage, but no elaborative information is provided regarding what had transpired.

AVE009012 lists the major diagnoses for ADRs in tabular form; US01-19841 was a fetal death, but no elaborative information is provided regarding what had transpired.

AVE009015 lists the major diagnoses for ADRs in tabular form; US01-20638 was a stillborn, but no elaborative information is provided regarding what had transpired.

Assessment: More information is needed regarding cases # US01-19841 & US01-19842 & US01-20638.

October 4, 1999 – December 29, 1999

13. ADR Fetal distress - High dosage of enoxaparin
{9:2,E}

AVE009024 depicts a newborn with one arm missing and webbing in the contralateral hand; this genetic anomaly is felt to be unrelated to prior Lovenox administration.

Jan. 4, 2000 to Mar. 31, 2000

14. Pregnancy Incident [AVE 009028]
ADR Death of Mother- Investigator considered event related to study drug.
{9:2,F}

AVE009028 depicts a woman with two prosthetic valves who died from endocarditis.

April 3, 2000 – May 31, 2000

15. Pregnancy Studies ADR [AVE 009039]
A study with Adverse Reaction events reported
{9:2,G}

AVE009036 depicts a man who hemorrhaged while on Lovenox.

AVE009049 also provides a literature-citation related to a case-report [edited], to wit:

> A literature report describes the use of Lovenox for thrombosis prophylaxis in pregnancy. The study period was from 1/1/1997 – 12/31/1998 and consisted of two groups, including 38 pregnancies in 35 patients. The first group included 27 patients whose risk of thrombosis increased by the pathological nature of the pregnancy (missed abortion, pre-eclampsia) and by the surgery performed as a consequence of this (surgical emptying of the uterus or Caesarian section). The second group consisted of 8 patients (including 11 pregnancies) who demonstrated congenital or acquired thrombophilia causing venous thrombosis or recurrent fetal loss.
>
> This report describes a patient (65 kg) in the second group who experienced hypertension of pregnancy, thrombocytopenia and complications with the fetus resulting in fetal retardation. She has a history of thrombophilia, mediated by anti-phospholipid antibody, and no history of thrombosis before pregnancy. She has also had seven abortions.
>
> During week 8 of pregnancy, treatment was initiated with Lovenox (20 mg daily) and was gradually increased to 40 mg daily in week 20, then 60 mg beginning from week 25 and continued for at least three days after termination of pregnancy. The patient developed premature labor on several occasions beginning from week 26. She also experienced hypertension in week 31. In week 32, Caesarian section had to be performed because of threatening fetal asphyxia. At some time during the course of treatment, the patient also developed thrombocytopenia (platelet counts between 60 x 10^{-9}/L and 100 x 10^{-9}/L). The newborn became a healthy survivor. In addition, macroscopic and microscopic infarcts were seen in the placenta after the delivery.
>
> The authors concluded that, in this patient population, Lovenox does not cause side effects, hemorrhagic diathesis or thrombocytopenia. It was also concluded that the risk for fetal loss, hypertension of pregnancy, premature placental separation and intrauterine retardation has been known to increase in the case of congenital thrombophilia. They did not implicate Lovenox as a contributor to the development of hypertension of pregnancy or fetal retardation.
>
> Pajor, A. Lukacsi, L., Sebestyen, A., Fontanyi, Z., Nemes, L., Paulin, F. Thrombosis prophylaxis in pregnancy using low molecular weight heparins. Magyar Noorvosok Lapja. Vol 62 (1999) No. 5, pp. 337-342.
>
> [See also Dossier # HU01-00008 (fetal retardation). See also Dossiers # HU01-00004, HU01-00005, HU01-00006 and HU01-00009 for other cases from this literature report.]

This is labeled (on the top of page #2) "Manufacturer Report Number HU01-00007." Yet, illustrative of the difficulty of tracing-back for this additional numbering system, the prior report is labeled (at the same spot) "GB01-06705." Therefore, in a good faith effort to discern what these additional reports might have constituted, previously flagged reports herein were re-checked for these MRN cross-references, to no avail. Noting #9 [*supra*], neither AVE 008974 nor AVE 008977 had any additional system starting "HU"; indeed, they were "GB01-02417" and "FR02-07892" respectively. [It is assumed that these numbers related to the countries which had reported the case, England and France.]

Assessment. Regarding the case report, it should be noted that the mother experienced unexplained thrombocytopenia; it could be ascribed neither to the pregnancy-related factors (including the anti-phospholipid syndrome) nor to the fetus-related factors (including the malformation); perhaps it arose during the peri-delivery time-frame, but insufficient data have been provided so as to address other diagnoses such as DIC. Therefore, this particular case report (including the pathology of the placenta) requires additional scrutiny. In addition, the entire set of case reports that informed the article published in the Hungarian literature [HU01-00004,5,6,9] requires additional scrutiny.

AVE01-009049 depicts another case report that followed the identical introduction as was provided regarding the aforementioned review article; the specifics follow:

> This report describes one patient (60kg) in the second group who became pregnant twice during the course of the study. She has a history of thrombophilia, mediated by anti-phospholipid antibody, spontaneous abortions and vena lienalis thrombosis before pregnancy. During the first pregnancy, while enrolled in the study, she developed portal vein thrombosis and placental separation which led to fetal death. During the second pregnancy, she experienced thrombocytopenia.
>
> First pregnancy: Treatment with Lovenox 20 mg daily was initiated before pregnancy and was continued for at least 3 days after termination of the pregnancy. During week 26, the patient developed asymptomatic, ultrasonically diagnosed portal vein thrombosis. In week 27, partial separation of the placenta occurred which led to fetal death. Macroscopic and microscopic infarcts were seen in the placenta after the delivery.
>
> Second pregnancy: Treatment with Lovenox had again been initiated before pregnancy and was continued for at least 3 days after termination (at 37 weeks, outcome not otherwise specified) or the pregnancy. Lovnox dose was gradually increased from 20 mg daily before week 20, then 40 mg in week 20 and 80 mg daily beginning from week 25. Thrombocytopenia developed (platelet counts between 60 x 10^{-9}/L and 100 x 10^{-9}/L) during treatment. Again, macroscopic and microscopic infarcts were seen in the placenta after the delivery.

> The authors concluded that Lovenox administered at a 20mg dose is insufficient for thrombosis prophylaxis in patients with high-risk for thrombosis, especially during the second half of pregnancy. It was also concluded that, in this patient population, Lovenox does not cause side effects, hemorrhagic diathesis or thrombocytopenia. The risk for fetal loss, hypertension of pregnancy, premature placental separation and intrauterine retardation has been known to increase in the case of congenital thrombophilia.

Assessment: [The rest of the filing mirrored the concluding section of its predecessor.] Here, although the case-specific conclusions are justified, the placental infarcts seem discordant to thrombocytopenia which is presumed to be immune (noting the underlying thrombophilia-syndrome). More information should be reviewed, such as the serial ANA and anti-platelet antibody testing, to probe these clinical linkages.

AVE01-009052 depicts still another case report that followed the identical introduction as was provided regarding the aforementioned review article; the specifics follow:

> This report describes a patient (80kg) in the second group who underwent Cadsarian section due to hypertension of pregnancy and fetal retardation. She has a history of Leiden V mutation, anti-phospholipid antibody, deep vein and cerebral sinus thrombosis before pregnancy. She has also had 2 spontaneous abortions.
>
> Before the planned pregnancy, the patient was switched from long-term Coumarin treatment to Calcium-Heparin and subsequently developed pulmonary embolism and thrombocytopenia (60×10^{-9}/L) during week 7 of pregnancy. At this time, treatment was changed to Lovenox 40 mg, S.C. daily. The patient's platelet count returned to normal after the change-over to Lovenox. During week 34 of pregnancy, a Caesarian section had to be performed because of exacerbating hypertension of pregnancy and fetal retardation. Macroscopic and microscopic infarcts were seen in the placenta after the delivery. The newborn became a healthy survivor.
>
> The authors concluded that, in this patient population, Lovenox does not cause side effects, hemorrhagic diathesis or thrombocytopenia. It was also concluded that the risk for fetal loss, hypertension of pregnancy, premature placental separation and intrauterine retardation has been known to increase in the case of congenital thrombophilia. They did not implicate Lovenox as a contributor to the development of hypertension of pregnancy or fetal retardation.

Assessment: [The rest of the filing mirrored the concluding section of its predecessors.] Here, although the case-specific conclusions are justified, the placental infarcts seem discordant to unexplained thrombocytopenia. More information should be reviewed.

16. Listing of 15-day Alerts Submissions (3/29/1999 - 3/28/2000)
Listing of Alert Submissions [AVE 009056]
Narrative Summary of Adverse Drug Experiences [AVE 009078]
Distribution of ADR by Body System [AVE 009132]
Narrative of Action Taken [AVE 009152]
{9:2,H}

The Listing includes Fetal Distress [GB01-05430 @ AVE 009062]; CNS Congenital Anomaly [US01-23736 @ AVE 009062]; Thrombosis and Fetal Death [ZA01-00209 @ AVE 009073]; and Cardiogenic Shock, Subacute Prosthetic Valve Thrombosis and Fetal Death [ZA01-00210 @ AVE 009073]. Page "23/23" is missing from this binder. {*n.b.*: Cardiogenic Shock, Subacute Prosthetic Valve Thrombosis and Fetal Death [ZA01-00210] occurred in November, 1999 and were cited previously as item #14.}

The Narrative Summary contains this elaborative information/analysis:

GB01-05430

Report Source: Spontaneous – Health Care Professional

This report describes a 35 year old woman underwent an emergent cesarean section secondary to *fetal distress* on 22-Feb-1999. The operation was successful, and the baby was healthy. The mother had complained of inflammation at enoxaparin injection sites and on the back of her thighs beginning 15-Feb-1999. These symptoms began to resolve after 25-Feb-1999. She had been receiving enoxaparin (40mg, subcutaneously, daily) from 14-Jan-1999 to 23-Feb-1999 for Factor V Leiden Antibodies. The reporter did not feel that there was any relationship between the fetal distress and enoxaparin therapy.

GB01-05569

Report Source: Spontaneous – Health Care Professional

This report refers to a 33 year old woman who gave birth on 8-Jun-1999 to a baby who was experiencing *"problems"* (not otherwise specified). At the time of last contact with the reporter, the infant was in the special care unit. The mother had been receiving enoxaparin pre and post-partum for an unknown indication.

{The baby born with congenital anomalies (US01-22842 @ AVE 009085) was cited previously as item #13. The case related to Cardiogenic Shock, Subacute Prosthetic Valve Thrombosis and Fetal Death [ZA01-00210] was cited previously as item #14.}

Two cases related to valvular thrombosis [ZA01-00209 and ZA01-00210] were noted to have prompted cessation of the study under which they had been treated ("High-Dose Lovenox vs. Standard Heparin/Coumadin," ENO-ZA-301, as per AVE 009109); Anti-Xa levels were reported in the latter case.] One adverse event reported during this year (3/29/1999 - 3/28/2000) was noted to have involved a fetus (AVE 009133). No action was taken relative to drug-labeling after this comprehensive study (AVE 009151).

Assessment: More information is needed related to the missing page #23, GB01-05569, and the omission of numerous case-discussions (summarized herein) from this précis.

August 1, 2000 – Nov. 28, 2000

17. ADRs - Draft of Article written with concern over enoxaparin
Anaphylactic Shock associated with Enoxaparin (Lovenox) Therapy: A Report of Three Cases, Review of the Literature and Discussion
Author: REDACTED [AVE 009160]
{9:2,I}

Of the three cases of anaphylaxis reported, one was in a pregnant woman; this report has no relationship with the issues related to trans-placental transmission of Lovenox.

AVE 009194 depicts a man who developed GI-bleeding.

AVE 009197 depicts a woman who developed hepatitis.

AVE 009200 depicts a newborn who developed ectodermal dysplasia.

AVE 009202 depicts a pregnant woman who developed a Mallory-Weiss tear.

AVE 009205 depicts a woman who died suddenly following a Lovenox IV-flush.

AVE 009207 depicts a man who had hemorrhagic shock and received Lovenox.

AVE 009209 depicts a 35 year-old woman who had a fetus who had an intrauterine death; "the Danish Medicines Agency considers the Death Fetal as possibly related to Lovenox." No further information was provided regarding the circumstances thereof.

Assessment: It is absolutely mandatory that further information be provided regarding the circumstances surrounding this event; particularly noting the governmental comment, there must have been a probe initiated and, thus, further data must have been accrued.

AVE 009211 depicts a newborn who had head bruising and bleeding from the umbilical stump; elevated PT/aPTT was treated successfully with Vitamin K without sequellae.

AVE 009213 depicts a man who had a GI-bleed.

December 1, 2000 to February 28, 2001

18. ADRs
{9:2,J}

AVE 009217 depicts a woman who developed *inter alia* azotemia.

AVE 009221 depicts a man who developed hemorrhage.

AVE 009226 depicts a man who developed *inter alia* hemo-pericardium.

AVE 009228 depicts a man who developed *inter alia* hemo-pericardium.

AVE 009230 depicts a man who developed *inter alia* hemo-pericardium.

AVE 009232 depicts a man who developed thrombocytopenia, skin necrosis and purpura.

AVE 009234 depicts a man who developed post-operative phlebitis.

AVE 009236 depicts a man who developed a post-operative pulmonary embolism.

AVE 009238 depicts a woman who developed post-operative phlebitis.

AVE 009240 depicts a man who developed a post-operative pulmonary embolism.

AVE 009242 depicts a man who developed a post-operative pulmonary embolism.

AVE 009244 depicts a man who developed post-operative phlebitis.

AVE 009246 depicts a woman who developed a post-operative pulmonary embolism.

AVE 009249 depicts a woman who died from a thrombosed mechanical valve.

AVE 009251 depicts a woman who developed GI-bleeding.

AVE 009256 depicts a woman who developed GI-bleeding.

AVE 009260 depicts a woman who developed an abdominal hematoma.

AVE 009263 depicts a woman who developed hyperkalemia.

AVE 009265 depicts a woman who developed anaphylactic shock.

AVE 009269 depicts a patient who had a sudden drop in Hemoglobin level.

18a. ADRs
{9:2,K}

AVE 009272 depicts a woman who developed *inter alia* amaurosis fugax.

AVE 009274 depicts a woman who developed a post-operative pulmonary embolism.

AVE 009277 depicts a woman who developed a Mallory-Weiss tear.

AVE 009279 depicts a woman who developed ovarian hyperstimulation.

AVE 009284 depicts a woman who had sudden death.

AVE 009286 depicts a patient who had sudden death.

AVE 009288 depicts a patient who had sudden death.

AVE 009290 depicts a man who had elevated liver enzymes.

AVE 009292 depicts a woman who developed cardiopulmonary arrest.

AVE 009295 depicts a woman who developed hepatitis.

March 7, 2001 to May 30, 2001

19. ADRs
{9:2,L}

AVE 009299 depicts a newborn who developed weight-loss.

AVE 009301 depicts a pregnant woman who had a fetus with a transiently absent heartbeat; she had a history of a positive anti-cardiolipin.

Assessment: More information is needed regarding this patient's course.

AVE 009303 depicts a post-partum woman who developed transient paralysis.

AVE 009305 depicts a three year-old boy who had developmental delays.

AVE 009307 depicts a woman who had a fetus with delayed growth.

Assessment: More information is needed regarding this patient's course.

AVE 009309 depicts a woman who had a fetus with delayed growth and Factor V Leiden.

Assessment: More information is needed regarding this patient's course.

AVE 009312 depicts a woman who had clots in her hands and Factor V Leiden.

AVE 009314 depicts a pregnant woman who died from a pulmonary embolism.

June 11, 2001

20. ADRs
{9:2,M}

AVE 009321 depicts a man who developed GI-bleeding.

AVE 009323 depicts a patient who developed an intracerebral hemorrhage.

AVE 009325 depicts a woman who developed a hematoma.

AVE 009327 depicts a man who developed an intracerebral hemorrhage.

AVE 009329 depicts a patient who developed a hematoma.

AVE 009331 depicts a patient who had hemorrhage.

AVE 009333 depicts a woman who had hemorrhage.

AVE 009337 depicts a woman who developed hematomas.

AVE 009340 depicts a woman who developed an elevated aPTT.

AVE 009343 depicts a woman who developed a subdural hematoma.

AVE 009345 depicts the result of a physician inquiry regarding an elevated aPTT.

AVE 009347 depicts a woman who developed back pain.

AVE 009349 depicts a man who developed a retroperitoneal hemorrhage.

AVE 009351 depicts a woman who developed an abdominal hematoma.

AVE 009353 depicts a man who developed a hematoma.

AVE 009355 depicts a woman who developed a hematoma.

AVE 009358 depicts a man who developed a hematoma.

AVE 009360 depicts a man who developed an intracerebral hemorrhage.

AVE 009363 depicts a patient who developed a hematoma.

AVE 009365 depicts a man who developed azotemia.

AVE 009367 depicts a newborn who had slow weight-gain.

AVE 009369 depicts a woman who developed conjunctivitis.

AVE 009371 depicts a patient who developed an elevated SGOT.

AVE 009373 depicts a man who developed incisional bleeding.

AVE 009375 depicts a man who developed elevated liver enzymes.

AVE 009378 depicts a man who developed pre-retinal macular hemorrhage.

AVE 009381 depicts a man who developed decreased saliva.

AVE 009383 depicts a woman who developed nausea.

AVE 009385 depicts a man who developed a hematoma.

AVE 009387 depicts a patient who developed anemia.

AVE 009389 depicts a woman who developed thrombocytosis.

AVE 009391 depicts a man who developed an increased INR.

AVE 009393 depicts a woman who developed an intracranial hemorrhage.

AVE 009396 depicts a man who developed thrombocytopenia.

AVE 009398 depicts a woman who developed a hematoma.

AVE 009400 depicts a woman who inadvertently received Lovenox.

AVE 009402 depicts a man who inadvertently received Lovenox.

AVE 009404 depicts a woman who developed an allergic reaction.

AVE 009406 depicts a man who developed an intracerebral hemorrhage.

AVE 009408 depicts a man who inadvertently received Lovenox.

AVE 009410 depicts a woman who developed hemorrhage in her eyes and lungs.

AVE 009412 depicts a patient who developed a rash.

AVE 009414 depicts a patient who developed phlebitis.

AVE 009416 depicts a patient who developed deep vein thrombosis

AVE 009418 depicts a patient who developed phlebitis.

AVE 009420 depicts a man who developed a seizure.

AVE 009422 depicts a patient who developed an intracerebral hemorrhage.

AVE 009424 depicts a woman who developed a retroperitoneal hematoma.

AVE 009426 depicts a man who developed thrombocytopenia.

AVE 009428 depicts a patient who developed phlebitis.

AVE 009430 depicts a man who developed eosinohilia.

AVE 009432 depicts a woman who developed orange palms.

AVE 009434 depicts a woman who developed an elevated PT.

AVE 009436 depicts a man who developed bruising.

AVE 009438 depicts a woman who developed angina.

AVE 009440 depicts a woman who developed GI-bleeding.

AVE 009442 depicts a man who developed local bleeding.

AVE 009445 depicts a man who developed bruises

AVE 009447 depicts a woman who developed a hematoma.

AVE 009449 depicts a woman who inadvertently received Lovenox.

AVE 009451 depicts a woman who developed bronchospasm.

AVE 009453 depicts a man who developed a retroperitoneal hematoma.

AVE 009455 depicts a woman who developed a pulmonary embolism.

AVE 009457 depicts a patient who developed incisional bleeding.

AVE 009459 depicts a man who developed hemorrhage.

AVE 009461 depicts a man who developed a hematoma.

AVE 009463 depicts a woman who also had pseudotumor cerebri.

AVE 009465 depicts a woman who inadvertently received Lovenox.

AVE 009467 depicts a patient who developed thrombocytosis.

AVE 009469 depicts a patient who inadvertently received Lovenox.

AVE 009471 depicts a patient who inadvertently received Lovenox.

AVE 009473 depicts a patient who experienced an elevated aPTT.

AVE 009475 depicts a patient who experienced an elevated aPTT.

AVE 009477 depicts a woman who experienced an elevated aPTT.

AVE 009479 depicts a patient who experienced an elevated aPTT.

AVE 009481 depicts a woman who developed a hematoma at an injection site.

AVE 009483 depicts a man who developed tracheal and gum hemorrhage.

21. ADRs
{10:3,A}

AVE 009485 depicts a woman who developed excessive bleeding.

AVE 009487 depicts a man who developed a retroperitoneal hematoma.

AVE 009489 depicts a woman who developed a retroperitoneal hematoma.

AVE 009491 depicts a man who developed thrombocytopenia.

AVE 009493 depicts a woman who developed insomnia.

AVE 009495 depicts a patient who developed hyperkalemia.

AVE 009497 depicts a woman who developed phlebitis.

AVE 009499 depicts a woman who developed hemorrhage.

AVE 009501 depicts a man who developed a hematoma.

AVE 009503 depicts a man who developed a retroperitoneal hematoma.

AVE 009505 depicts a man who developed a hematoma.

AVE 009507 depicts a woman who had low progesterone levels.

AVE 009510 depicts a woman who developed HIT.

AVE 009512 depicts a woman who developed leucopenia.

AVE 009514 depicts a patient who developed a retroperitoneal hematoma.

AVE 009516 depicts a woman who developed internal bleeding.

AVE 009518 depicts a man who developed internal bleeding.

AVE 009521 depicts a man who developed an elevated clotting time.

AVE 009523 depicts a woman who developed sleeping disorders.

AVE 009525 depicts a patient who developed a hematoma.

AVE 009527 depicts a woman who developed a retroperitoneal hematoma.

AVE 009529 depicts patients who developed hemorrhage.

AVE 009531 depicts a patient who developed a decreased insulin requirement.

AVE 009533 depicts a woman who developed *inter alia* hematomas.

AVE 009536 depicts a woman who inadvertently received Lovenox.

AVE 009538 depicts a woman who developed a retroperitoneal hematoma.

AVE 009540 depicts a man who developed a hematoma.

AVE 009542 depicts a man who developed a epidural hematoma.

AVE 009544 depicts a woman who developed a hematoma.

AVE 009546 depicts a woman who developed a hematoma.

AVE 009550 depicts a man who developed an intrathecal hematoma.

AVE 009552 depicts a man who developed an intrathecal hematoma.

AVE 009554 depicts a man who developed pulmonary emboli.

AVE 009556 depicts a woman who developed *inter alia* a numb tongue.

AVE 009558 depicts a woman who failed to achieve *in vitro* fertilization.

AVE 009560 depicts a woman who failed to achieve *in vitro* fertilization.

AVE 009562 depicts a patient who developed a hematoma.

AVE 009564 depicts a woman who developed return of her menses.

AVE 009566 depicts a man who developed a hematoma.

AVE 009569 depicts a man who developed HIT.

AVE 009571 depicts a woman who developed chills.

AVE 009573 depicts a patient who developed a swollen tongue.

AVE 009575 depicts a patient who developed a retroperitoneal hematoma.

AVE 009577 depicts a man who developed a retroperitoneal hematoma.

AVE 009580 depicts a patient who developed phlebitis.

AVE 009582 depicts a man who developed a pulmonary embolism.

22. ADRs
{10:3,B1}

AVE 009586 depicts a woman who developed hemorrhage.

AVE 009588 depicts a woman who developed acral parasthesias.

AVE 009590 depicts a man who developed bruises.

AVE 009592 depicts a fetal death in a woman with two prior fetal deaths and two coagulopathies (positive anti-cardiolipin and Factor V Leiden).

Assessment: This case was felt by the neonatologist not to be Lovenox-related.

AVE 009594 depicts a fetal death in a woman with two coagulopathies (positive anti-cardiolipin and Factor V Leiden).

Assessment: This case was felt by the neonatologist not to be Lovenox-related.

AVE 009596 depicts a man with prolonged bleeding.

AVE 009598 depicts a woman with a retroperitoneal hematoma.

AVE 009600 depicts a patient with a retroperitoneal hematoma.

AVE 009602 depicts a woman who developed alopecia.

AVE 009604 depicts a woman who developed confusion.

AVE 009606 depicts a man who developed bleeding.

AVE 009608 depicts a patient who developed HIT.

AVE 009610 depicts a woman who developed GI bleeding.

AVE 009612 depicts a woman who developed GI bleeding.

AVE 009614 depicts a man who developed a retroperitoneal hematoma.

AVE 009616 depicts a woman who developed hemorrhage.

AVE 009618 depicts a patient who developed HIT.

AVE 009620 depicts a man who developed a hematoma.

AVE 009622 depicts three patients who developed hematomas.

AVE 009624 depicts a man who developed increased hemorrhagic chest tube drainage.

AVE 009626 depicts a patient who had excessive bleeding.

AVE 009628 depicts a patient who developed a catheter sheath hematoma.

AVE 009630 depicts a patient who developed HIT.

AVE 009632 depicts a man who developed bleeding.

AVE 009635 depicts a woman who developed oozing.

AVE 009637 depicts a man who developed a hematoma.

AVE 009639 depicts a man who developed excess thirst.

AVE 009641 depicts a woman who developed leukopenia.

AVE 009643 depicts a man who developed petechiae.

AVE 009645 depicts a man who developed GI bleeding.

AVE 009647 depicts a woman who developed an intracranial hematoma.

AVE 009649 depicts a woman who developed a retroperitoneal hematoma.

AVE 009652 depicts a man who developed an intracranial hematoma.

AVE 009654 depicts a man who developed dyspnea.

AVE 009656 depicts a patient who developed a hematoma.

AVE 009659 depicts a woman who had intraoperative hemorrhage.

AVE 009660 depicts a woman who developed a hematoma.

AVE 009663 depicts a patient who developed loose tendons.

AVE 009664 depicts two patients who developed hematomas.

AVE 009666 depicts two patients who developed hematomas.

AVE 009668 depicts a woman who developed bleeding.

AVE 009670 depicts two patients who developed bleeding.

AVE 009672 depicts two patients who developed bleeding.

AVE 009674 depicts two women who developed bleeding.

AVE 009676 depicts a man who developed phlebitis.

AVE 009677 depicts a woman who developed blotches.

AVE 009679 depicts a woman who developed migraine headaches.

AVE 009680 depicts a woman who developed skin necrosis

AVE 009682 depicts a man who developed arthritis.

AVE 009683 depicts a man who developed anxiety.

AVE 009684 depicts a woman who developed a rash.

AVE 009686 depicts patients who became febrile.

AVE 009687 depicts patients who became febrile.

AVE 009688 depicts a woman who developed a hematoma.

AVE 009690 depicts a woman who developed a retroperitoneal hematoma.

AVE 009692 depicts a patient who developed HIT.

AVE 009694 depicts a woman who developed a thrombosed mechanical valve.

AVE 009695 depicts a woman who developed hemorrhage.

AVE 009696 depicts a patient who developed hemorrhage.

AVE 009697 depicts a woman who developed hemorrhage.

AVE 009699 depicts a patient who developed a rash.

AVE 009700 depicts a man who developed nodules.

AVE 009701 depicts a patient who developed hyperkalemia.

AVE 009703 depicts a woman who developed a hematoma.

AVE 009705 depicts a man who developed a hematoma.

AVE 009706 depicts a patient who developed bleeding.

AVE 009707 depicts a woman who developed bleeding.

AVE 009710 depicts a man who developed hemorrhage.

AVE 009712 depicts a woman who developed headaches.

AVE 009715 depicts a woman who developed a flushed-sensation.

AVE 009716 depicts a woman who developed a flushed-sensation.

AVE 009717 depicts a woman who developed arm weakness.

AVE 009718 depicts a woman who developed tinnitus.

AVE 009719 depicts a woman who developed internal bleeding.

AVE 009723 depicts a woman who developed internal bleeding.

AVE 009725 depicts a man who developed internal bleeding.

AVE 009727 depicts a man who developed GI-Bleeding.

AVE 009729 depicts a man who developed HIT.

AVE 009731 depicts a man who developed localized bleeding.

AVE 009733 depicts a man who developed GI-Bleeding.

23. **Table 1: Serious and Unexpected Events**, March 29, 2000 to March 28, 2001 {10:3,B2}

System Organ Class: Pregnancy, puerperium and perinatal conditions			
Report Number	**Follow-up**	**Submitted To FDA**	**Clinical Term as Reported** ***MedDRA Preferred Term*** **Reporter (if directly reported to FDA)**
200021089EU	I	01-NOV-2000	DEATH FOETAL *INTRA-UTERINE DEATH*
200112099US	I	20-MAR-2001	NO FETAL HEARTBEAT *FOETAL DISTRESS SYNDROME*
00004	I	19-MAY-2000	PLACENTAL INFARCTION *RETAINED PLACENTA OR MEMBRANES*
-00004	F-1	13-OCT-2000	PLACENTAL INFARCTION *RETAINED PLACENTA OR MEMBRANES*
HU01-00005	I	19-MAY-2000	FETAL RETARDATION *FOETAL MATURATION IMPAIRED* HYPERTENSION OF PREGNANCY *PREGNANCY INDUCED HYPERTENSION* PLACENTAL INFARCTS *RETAINED PLACENTA OR MEMBRANES*
HU01-00005	F-1	12-OCT-2000	FETAL RETARDATION *FOETAL MATURATION IMPAIRED* HYPERTENSION OF PREGNANCY *PREGNANCY INDUCED HYPERTENSION* PLACENTAL INFARCTS *RETAINED PLACENTA OR MEMBRANES*

457

System Organ Class: Pregnancy, puerperium and perinatal conditions			
Report Number	**Follow-up**	**Submitted To FDA**	**Clinical Term as Reported** ***MedDRA Preferred Term*** **Reporter (if directly reported to FDA)**
HU01-00006	I	19-MAY-2000	FETAL RETARDATION *FOETAL DAMAGE NOS*
HU01-00007	I	19-MAY-2000	PLACENTAL INFARCTS *PLACENTAL DISORDER NOS*
-00008	I	19-MAY-2000	FETAL RETARDATION *FOETAL DAMAGE NOS*
458 23747	I	24-MAY-2000	PREMATURE RUPTURE OF MEMBRANES *COMPLICATIONS OF PREGNANCY NOS*

The Follow-Up column has abbreviations ["I" and "F-1"] which are not defined. Also, the numbering-system does not cross-reference specific cases; a cross-walk would, thus, need to be surmised (based on the case reviews). What is vital to appreciate, here, is the absence of any follow-up information when even the diagnosis of "fetal damage" exists. [The "Americanized" spelling of "foetus" is used herein ("fetus"), just as the "Lovenox" brand-name has been used instead of the less-familiar generic-term "Enoxaparin."]

Assessment: What is particularly remarkable both in this physician's distillation and the tabular presentation of the data is the absence of a consistent database. For example, pathologic assessment of the placenta is not consistently reported, and this is information that could have been acquired in "real time" when reports of adverse actions arrived. Even if other explanations for any given finding might be conjured—such as a conjoint "abruption placenta"—the inability to "reach" even this rudimentary level of analysis impugns the ability to claim that the public-protection role of the pharmaceutical house has been upheld. This is not a pass-through activity; rather, it is to be based on the best measured judgments regarding the need to maintain an academic/clinical level of inquiry that would not wish to miss any potentially-toxic drug-effect. That the public trust in the FDA is predicated on the maxim "*primum non nocere*" is central to its basic charge; although efficacy data are accrued and dutifully reported, toxicity data are emphasized. Further analysis of this entire data-set is segregated to a distinct site in this report, *infra*.

****Inasmuch as the "yield" of relevant patient-reports has been relatively low when this comprehensive approach has been followed, a more abbreviative summary is now to be provided; a case-by-case analysis can be provided as needed. Clearly established, here, is the fact that most of the realistic complications (excluding the plethora of anecdotes) are hemorrhage-related; this is intuitive when one considers the drugs basic effects (and, of course, is consistent with the episode of bleeding experienced in this case).****

24. **Table 2: Serious and Expected Events**, March 29, 2000 to March 28, 2001 (10:3,B3}

System Organ Class:	Pregnancy, puerperium and perinatal conditions	
Report Number Submitted To FDA	**Follow-up**	**Clinical Term as Reported *MedDRA Preferred Term* Reporter (if directly reported to FDA)**
200113096US	I	FETAL DEATH *INTRA-UTERINE DEATH*
200113097US	I	FETAL DEATH *INTRA-UTERINE DEATH*
25235 tted: 24-JUL-2000	I	INTRAUTERINE FETAL DEATH *INTRA-UTERINE DEATH*
25235 itted: 13-OCT-2000	F-1	INTRAUTERINE FETAL DEATH *INTRA-UTERINE DEATH*

Assessment: It is surprising that these findings were "expected" in contrast to the prior tabulation, when the diagnoses are essentially indistinguishable. Indeed, in the absence of any notation that there might have been a concomitant congenital anomaly to explain fetal-demise [again, recognizing the limited capacity to cross-reference the clinical data], why these data are also sparse (for example, again not having pushed for documentation of pathological examination of the placenta) raises credibility questions regarding the intensity of "intellectual curiosity" which should be magnified under these circumstances. Noting the discrepancy between the numbers of administered-dosages and case-reports, pursuit of but any one case carries the potential to affect the global marketplace.

25. Index, Table 3: Non-Serious Domestic Spontaneous Events, March 29, 2000 to March 28, 2001
{10:3,B4}

[There is nothing on this table that relates to the potential for any degree of fetal damage.]

26. **Index, Table 4: SU Events by System Organ Class**, March 29, 2000 to March 28, 2001
{10:3,B5}

The table on the next page depicts "Pregnancy, Puerperium and Perinatal Conditions." All except #3 and #4 were filed after only one initial report (with the others filed through two initial reports), and none of them were filed in conjunction with a follow-up report.

Intra-uterine death
Foetal distress syndrome
Foetal damage NOS
Retained placenta or membranes
Pregnancy induced hypertension
Complications of pregnancy NOS
Foetal maturation impaired
Placental disorder NOS

Assessment: As noted *supra*, these groups appear almost arbitrary (and, if nothing else, carry tremendous capacity to overlap). All are better perceived as "syndromes" rather than "diagnoses," for each can be explained (in isolation) by either myriad or a unitary underlying pathogenesis. It is also noted that another category contrasts with this status; "Congenital and Familial/Genetic Disorders" are distinguished "with a difference" and, therefore, have not even been listed herein. Having adopted a self-limited approach to discerning what might have caused these findings clearly emerges as a pervasive concern.

27. **Index, Table 5: SE, NE, & NU Events by System Organ Class**, March 29, 2000 to March 28, 2001
{10:3,B6}

Assessment: Three items are in the "Pregnancy, Puerperium and Perinatal Conditions" section: Intrauterine Death (3 initial reports), Complications of Pregnancy NOS (2) and Feeding Problems in Newborn (1). None had generated follow-up reports, and there was again no effort to cross-walk the databases because the specific cases comprising each listing were not provided. Why the higher number of such conditions in other tables was diminished was not explained; again, absent an analytic component, it was not possible to discern what fundamental criteria were employed when these tables were being compiled.

28. Index, Table 6: **Events Resulting in Death**, March 29, 2000 to March 28, 2001
{10:3,B7}

Assessment: Two listings are in the "Pregnancy, Puerperium and Perinatal Conditions" section: "Intrauterine Fetal Death" related to US01-25235; one with follow-up "I" (submitted 7/24/2000) and another with follow-up "F-1" (submitted 10/13/2000). Thus, as noted repeatedly, why cases were consistently deleted is unclear.

29. **Listing of 15-day Alerts** Submitted, March 29, 2000 to March 28, 2001
{10:3,B8}

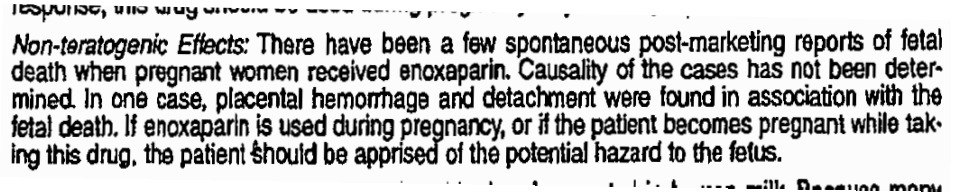
Assessment: This listing of all cases that would be perceived as potentially relevant, again contains information that cannot be correlated with that depicted elsewhere.

HU01-00004	THROMBOSIS PORTAL VEIN
	PLACENTAL DISORDER
	FOETAL DEATH
	THROMBOCYTOPENIA
	PLACENTAL DISORDER
J01-00005	HYPERTENSION
	PLACENTAL DISORDER
HU01-00006	FETAL DISORDER
HU01-00007	HYPERTENSION
	THROMBOCYTOPENIA
	PLACENTAL DISORDER
HU01-00008	FETAL DISORDER

30. **Index of FDA 3500's** March 29, 2000 to March 28, 2001
{10:3,B9}

Assessment: Two tables are provided. The first is an index of cases, and the second is a compilation of the cases by body-system. The first includes US01-24659 (Fetal Death); follow-up reports were generated for only seven cases. The second includes one Fetal Disorder, which was then calculated (with whatever import) as 3.57% of all events in this body system, 0.5% of all events, one patient, 4% of patients in this body system, and 1.22% of all patients. [The "body system" was "body as whole."] Again, how it is discerned that there was only one "Fetal Death" is not rectified with other data-sources.

31. **Narrative Summary** [AVE 009982]
Insert Rev. 1/2000 [AVE 009984]
{10:3,B10}



Non-teratogenic Effects: There have been a few spontaneous post-marketing reports of fetal death when pregnant women received enoxaparin. Causality of the cases has not been determined. In one case, placental hemorrhage and detachment were found in association with the fetal death. If enoxaparin is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Assessment: This set of recommendations is definably deficient, for it states that only one case of placental hemorrhage and detachment had been discerned; multiple cases of placental hemorrhage had been reported, not withstanding the lack of due diligence when pursuing the need for follow-up information. The degree to which the stated hazard has been captured in marketing of this agent is to be addressed following the data-analysis.

June 1, 2001 to August 30, 2001

32. Selected ADLs
{11:4,A}

AVE 009993 depicts an elective second-trimester abortion performed because a fetus had a cleft lip and a congenital diaphragmatic hernia.

Sept. 5, 2001 to Dec. 28, 2001

33. Selected ADRs – Pregnancy, fetal death related
{11:4,B}

AVE 010007 depicts a woman who developed cerebral phlebitis while pregnant.

AVE 010009 depicts a 30 year-old woman with Factor V Leiden (and Gilbert's Disease) who experienced a retroplacental hematoma (and, thus, fetal loss) @ 35 weeks'gestation. At laparotomy, the coagulopathy had worsened (with thrombocytopenia, azotemia and "hepatic cytolysis"), revealing "a large hemoperitoneum and perihepatic hematoma." Transfusions [pRBCs (17 units), FFP (17 units), salt-poor albumin (3) and platelets (3)] yielded improvement during the subsequent two days, but no follow-up report exists. "Lovenox was considered as a suspect drug with a doubtful imputability."

Assessment: *Au contraire*, there is no doubt that the spontaneous hemorrhage was caused by the Lovenox, probably triggering DIC via systemic release of products of conception. The Lovenox was both "suspect" and "imputable." [To be discussed *infra*, also, is the phenomenon of hemorrhage between the blood circulations of mother and fetus.]

AVE 010011 depicts a 9 day-old boy with clonic left arm/leg movements.

AVE 010015 depicts a woman who experienced a spontaneous first-trimester abortion.

AVE 010017 depicts two patients with prolonged aPTT.

Jan. 2, 2002 to May 2, 2002

34. Pregnancy related ADR [AVE 010020]
Pregnancy related ADR [AVE 010022]

Case Report: Massive choroidal hemorrhage associated with LMW heparin therapy
Author: M. Neudorfer
Source: Blood Coagulation and Fibrinolysis 2002, 13: 257 – 259
[AVE 010033]

Pregnancy related ADR [AVE 010038]
Pregnancy related ADR [AVE 010044]
Pregnancy related ADR [AVE 010048]
Pregnancy related ADR [AVE 010050]
{11:4,C}

AVE 010020 depicts a woman who delivered a normal baby @ 32 weeks' gestation; although the initial Apgar was "1" (without specifying the number of minutes of life), there is no evidence of a hemorrhagic phenomenon (and the mother had used marijuana).

AVE 010024 depicts a woman who developed hemorrhage.

AVE 010027 depicts a woman who developed anemia.

AVE 010030 depicts a woman who developed subchoroidal hemorrhage.

AVE 010033 depicts an article about subchoroidal hemorrhage ascribed to Lovenox because "the acute onset of the bleeding with the close proximity to the beginning of Lovenox therapy makes our diagnosis the only probable diagnosis for this patient." The authors found one additional case-report of this association and surmised rationale.

Assessment: This is an example of hemorrhage associated with Lovenox in which the independent authors conclude a cause/effect relationship due both to knowledge of how the drug works and to awareness of tight chronologic contiguity. It is this level of basic "clinical suspicion" that would reasonably warrant reporting and further investigation. This is what these authors chose to do, and this is what Aventis is expected to do.

AVE 010035 depicts a woman who developed abdominal wall hemorrhage.

AVE 010038 depicts a newborn with initial distress; no further data were provided.

Assessment: This baby's experience also could have had a hemorrhagic component and, thus, inquiry regarding the particulars of what transpired should have been initiated.

AVE 010040 depicts a woman who developed bleeding after having fallen.

AVE 010042 depicts Fetal Demise @ 14 weeks' gestation; Coumadin had been replaced by Lovenox three weeks prior. The patient had a downhill course (cardiac, basically); there was no hemorrhagic component to what transpired during the pregnancy.

AVE 010046 depicts a woman who developed hemorrhage.

[AVE 010048 recapitulates the case noted @ AVE 010042.]

[AVE 010050 recapitulates the case noted @ AVE 010011.]

May 23, 2002

35. –
{11:4,D}

AVE 010053 depicts a woman who developed a subdural hematoma.

AVE 010055 depicts a woman who developed GI-Bleeding.

AVE 010059 depicts a man who developed dizziness.

AVE 010060 depicts a man who developed intracerebral hemorrhage.

AVE 010063 depicts a woman who developed intracerebral hemorrhage.

AVE 010065 depicts a woman who developed hemorrhage.

AVE 010065 depicts multiple patients who developed hemorrhage.

June 11, 2002 to July 30, 2002

36. Pregnancy related ADR [AVE 010070]
Pregnancy related ADR [AVE 010072]
Fetal Death ADR [AVE 010077]
{11:4,E}

AVE 010070 depicts a low birth-weight baby with some developmental delays.

AVE 010072 depicts a woman who developed a firs-trimester miscarriage.

AVE 010074 depicts a man who developed increased liver enzymes.

AVE 010077 depicts a woman who experienced a spontaneous second-trimester abortion.

Aug. 2, 2002 to Dec. 30, 2002

37.	Pregnancy related ADR	[AVE 010085]
	Pregnancy related ADR	[AVE 010087]
	Pregnancy related ADR	[AVE 010089]
	Pregnancy related ADR	[AVE 010091]
	Pregnancy related ADR	[AVE 010093]
	Pregnancy related ADR	[AVE 010095]
	Fetal related ADR	[AVE 010097]
	Fetal related ADR	[AVE 010100]
	Pregnancy related ADR	[AVE 010104]
	{11:4,F}	

AVE 010080 depicts a man who developed hemorrhage.

AVE 010083 depicts a woman who experienced a spontaneous first-trimester abortion.

AVE 010087 depicts a newborn with craniosynostosis.

AVE 010089 depicts a newborn with multiple fused digits of hands and feet.

AVE 010091 depicts a newborn who developed a dysrhythmia.

AVE 010093 depicts a woman who experienced a spontaneous second-trimester abortion.

AVE 010095 depicts a woman who developed *abruptio placentae*.

AVE 010097 depicts a low birth-weight baby with some developmental delays.

AVE 010100 depicts a newborn who developed some developmental delays.

AVE 010102 depicts a newborn who developed some developmental delays.

AVE 010104 depicts a newborn who developed some developmental delays.

January 3, 2003 to May 28, 2003

38.	Pregnancy related ADR	[AVE 010107]
	Pregnancy related ADR	[AVE 010109]
	Pregnancy related ADR	[AVE 010112]
	Fetal death ADR	[AVE 010114]
	Pregnancy related ADR	[AVE 010116]
	Pregnancy related ADR	[AVE 010118]
	Pregnancy related ADR	[AVE 010120]
	{11:4,G}	

AVE 010107 depicts a newborn with hydrocephalus.

AVE 010109 depicts a woman who developed *abruptio placentae*.

AVE 010112 depicts a woman who developed missed abortion.

AVE 010114 depicts a woman who delivered a stillborn infant.

AVE 010116 depicts a newborn who had a low birth-weight.

AVE 010118 depicts a woman who developed missed abortion.

AVE 010120 depicts an infant who experienced a Caesarian section birth.

May 29, 2003 to Sept. 29, 2003

39.	Pregnancy related ADR	[AVE 010123]
	Pregnancy related ADR	[AVE 010125]
	Pregnancy related ADR	[AVE 010129]
	Fetal related ADR	[AVE 010131]
	Pregnancy related ADR	[AVE 010133]
	Fetal related ADR	[AVE 010135]
	Pregnancy related ADR	[AVE 010137]
	Pregnancy related ADR	[AVE 010140]
	Pregnancy related ADR	[AVE 010142]
	Fetal related ADR	[AVE 010144]
	Pregnancy related ADR	[AVE 010147]
	{11:4,H}	

AVE 010123 depicts a woman who experienced a spontaneous abortion.

AVE 010125 depicts a woman who developed *inter alia* a burning sensation.

AVE 010129 depicts a woman who delivered a baby prematurely.

AVE 010133 depicts a woman who delivered a stillborn baby.

AVE 010135 depicts a newborn who died from hemoperitoneum by rupture of hepatic capsule and placental lesions with multiple infarctions; the baby experienced bradycardia. The baby's mother had a history of anti-phospholipid syndrome.

Assessment: The placental infarctions can't be reflexly ascribed to the autoimmune state. Unlike many of the (unflagged, here) abortion-related cases (in which the placenta is not routinely examined) this case entailed a term-birth. Therefore, both in isolation and related to other cases, the placental pathology could be explained by use of Lovenox.

AVE 010137 depicts a premature birth (at 35 weeks' gestation).

AVE 010140 depicts a woman who experienced a spontaneous abortion.

AVE 010142 depicts a woman with fibroids who delivered a child prematurely.

AVE 010147 depicts a woman who experienced a spontaneous abortion.

October 1, 2003 to December 31, 2003

40.	Fetal Death ADR	[AVE 010150]
	Pregnancy related ADR	[AVE 010153]
	Fetal related ADR	[AVE 010155]
	Pregnancy related ADR	[AVE 010157]
	Pregnancy related ADR	[AVE 010159]
	Pregnancy related ADR	[AVE 010161]
	Fetal death ADR	[AVE 010164]
	Fetal related ADR	[AVE 010166]
	Pregnancy related ADR	[AVE 010174]
	Pregnancy related ADR	[AVE 010176]

Article: **Use of low molecular mass heparin (enoxaparin) in newborn infants: a prospective cohort study of 62 patients**
Author: REDACTED
Source: Arch Dis Child Fetal Neonatol Ed 2003; 88: F365 – F370
[AVE 010168]
{11:4,I}

ADR 010150 depicts a woman who suffered a spontaneous second-trimester abortion.

AVE 010153 depicts a woman who had a premature delivery of a baby who had an intracerebral hemorrhage, but a follow-up report stated she did not take Lovenox.

AVE 010157 depicts a woman who developed blood "pooling."

AVE 010159 depicts a woman who developed pre-eclampsia.

AVE 010161 depicts a woman who developed *abruptio placentae* and fetal demise.

Assessment: The report ends with this statement: "The physician assessed the causal relationship between events and treatment with Lovenox as 'not associated' but mentioned that a third party had expressed a suspicion of causal relationship between premature abruption of placenta and treatment with Lovenox." It would be desirable to know the identity of the initial physician—particularly if he/she is an Aventis employee—and the rationale for having reached this all-encompassing conclusion.

AVE 010164 depicts an infant who died from a thrombosed obstruction of a modified Blalock-Taussig shunt.

AVE 010166 depicts an infant who developed a stroke after he underwent extracorporeal membrane oxygenization.

AVE 010168 constitutes an article about using Lovenox in newborns.

AVE 010174 depicts a woman who delivered a normal baby, and then developed parasthesias.

AVE 010176 depicts a woman who experienced a spontaneous first-trimester abortion.

Distillations

The observations gleaned from the comprehensive record review are now recounted:

AVE008484 depicts a 60 year-old woman who died in the post-op setting (knee surgery) from heparin-induced thrombocytopenia ["HIT"], after a cerebral hemorrhage. It is noted that the clinical summary has potentially-contradictory information, but the thrust of the case seems to be that the patient developed this complication promptly after the drug had been initiated (not withstanding performance of a non-essential cholecystectomy). Here, the drug had been given for nine days (inclusive) before the CVA presented, and it was given for an additional two days before HIT was suspected (and, presumably, the drug was then stopped). There is no citation of concomitant Coumadin, although the labs suggest that the predominant effect was on platelets (10K nadir) and not PT/aPTT.

Assessment: Ultimately, because dosage-related information has not been provided, determining the cause of the HIT (for example, whether it was idiosyncratic vs. whether the risk thereof was enhanced by some unreported factor) cannot be definitively ID'ed.

AVE008506 depicts a woman who developed DVT during her third month of pregnancy; it started in the sural vein and extended into the iliac vein before causing a PE. Thus, she was given unfractionated heparin for a month, daleparin for a month, and then Lovenox (40 mg daily during months #5-7 and 20 mg daily during month #8). Finally, "At week #37 (after last menstrual period date), placental detachment was observed with hemorrhage, needing delivery by Caesarian Section. Death *in utero*. No maternal complication." [This report was provided through a French drug subsidiary.]

Assessment: ***This case provides a precise model for what transpired in the instant case, even featuring the dosage-decrement and the potential for transplacental transmission.***

Spontaneously Reported Cases of Thrombocytopenia Associated with Enoxaparine Administration [AVE 008513]
Patient Index Summary [AVE 008519]
Additional ADRs [AVE 008529]
FETAL DEATH incident [AVE 008530]
{8:1,A3}

These relate to a HIT-pathogenesis, noting that 6/17 patients had confirmatory lab studies (while the others lacked a DIC-component) and 4/5 of the references related to HIT (while the first was an internal New Drug Application citation). Six patients died, two with intracerebral hemorrhage from severe thrombocytopenia (71 and 90 years of age). Regarding the fraternal twins, data were not reported (on the appended table) related to three criteria (prior use of either heparin or LMWH, prior thrombocytopenia, lab testing).

Assessment: Not withstanding the rationalization that this is an uncommon occurrence, this documents the fact that at least once instance of a transplacental event transpired.

AVE 008530 depicts a "Fetal Death" incident involving a 35 year-old woman who had previously been heparinized during her first pregnancy (with a normal outcome thereof).

Assessment: There is a dearth of specific data regarding the chronology of anti-Xa tests; apparently, only one (normal) value was acquired, early in the patient's six-day course. Because the fetus had experienced intrathoracic hemorrhage, the conclusion was justified that there was linkage; that the hypotrophic placenta had shown infarcts (of varying age) provides an additional clue to a possible pathogenesis of what had suddenly transpired.

AVE008968 depicts a tabular listing of aforementioned ADRs, including "fetal death"; because the aforementioned case does not fall within this time-frame [3/29/96 – 3/28/97], it cannot be assumed that Manufacturer Control Number 01-011211 cites this entry.

Assessment: The information related to MCN 01-011211 needs to be reviewed.

AVE008974 depicts what appears to have been a spontaneous abortion of a 2# fetus @ 36 weeks' gestation (upon which there was an unremarkable autopsy) of a 22 year-old woman who had been taking Lovenox for an unknown period at an unknown dosage.

Assessment: There is insufficient information upon which to base a definitive judgment but, in light of the fact that the fetus demonstrated no hemorrhage, it is possible to be suggestive that there was no relationship between this agent and what later transpired. For example, there is no information regarding whether there was any placental anomaly.

AVE008977 depicts a 33 year-old prime-ip who experienced pyelonephritis-induced sepsic-shock/DIC at the end of the third trimester; six months hence, because ultrasound showed hydrocephalus, there was a therapeutic abortion. Autopsy showed hemorrhage, but it is likely this was due to the acute coagulopathy rather than due to the Lovenox.

Assessment: There is insufficient information upon which to base a definitive judgment but, in light of the fact that the fetus demonstrated hemorrhage, it is not possible to be conclusive that there was no relationship between this agent and what later transpired. For example, there is no information regarding whether there was any placental anomaly, and it is therefore possible that the subsequent findings were caused by the Lovenox.

AVE009001 lists the major diagnoses for ADRs in tabular form; US01-19841 was a miscarriage, but no elaborative information is provided regarding what had transpired.

AVE009012 lists the major diagnoses for ADRs in tabular form; US01-19841 was a fetal death, but no elaborative information is provided regarding what had transpired.

AVE009015 lists the major diagnoses for ADRs in tabular form; US01-20638 was a stillborn, but no elaborative information is provided regarding what had transpired.

Assessment: More information is needed regarding cases # US01-19841 & US01-19842 & US01-20638.

AVE009049 also provides a literature-citation related to a case-report [edited], to wit:

> [deleted]

This is labeled (on the top of page #2) "Manufacturer Report Number HU01-00007." Yet, illustrative of the difficulty of tracing-back for this additional numbering system, the prior report is labeled (at the same spot) "GB01-06705." Therefore, in a good faith effort to discern what these additional reports might have constituted, previously flagged reports herein were re-checked for these MRN cross-references, to no avail. Noting #9 [*supra*], neither AVE 008974 nor AVE 008977 had any additional system starting "HU"; indeed, they were "GB01-02417" and "FR02-07892" respectively. [It is assumed that these numbers related to the countries which had reported the case, England and France.]

Assessment. Regarding the case report, it should be noted that the mother experienced unexplained thrombocytopenia; it could be ascribed neither to the pregnancy-related factors (including the anti-phospholipid syndrome) nor to the fetus-related factors (including the malformation); perhaps it arose during the peri-delivery time-frame, but insufficient data have been provided so as to address other diagnoses such as DIC. Therefore, this particular case report (including the pathology of the placenta) requires additional scrutiny. In addition, the entire set of case reports that informed the article published in the Hungarian literature [HU01-00004,5,6,9] requires additional scrutiny.

AVE01-009049 depicts another case report that followed the identical introduction as was provided regarding the aforementioned review article; the specifics follow:

[deleted]

Assessment: [The rest of the filing mirrored the concluding section of its predecessor.] Here, although the case-specific conclusions are justified, the placental infarcts seem discordant to thrombocytopenia which is presumed to be immune (noting the underlying thrombophilia-syndrome). More information should be reviewed, such as the serial ANA and anti-platelet antibody testing, to probe these clinical linkages.

AVE01-009052 depicts still another case report that followed the identical introduction as was provided regarding the aforementioned review article; the specifics follow:

[deleted]

Assessment: [The rest of the filing mirrored the concluding section of its predecessors.] Here, although the case-specific conclusions are justified, the placental infarcts seem discordant to unexplained thrombocytopenia. More information should be reviewed.

The Listing includes Fetal Distress [GB01-05430 @ AVE 009062]; CNS Congenital Anomaly [US01-23736 @ AVE 009062]; Thrombosis and Fetal Death [ZA01-00209 @ AVE 009073]; and Cardiogenic Shock, Subacute Prosthetic Valve Thrombosis and Fetal Death [ZA01-00210 @ AVE 009073]. Page "23/23" is missing from this binder. {*n.b.*: Cardiogenic Shock, Subacute Prosthetic Valve Thrombosis and Fetal Death [ZA01-00210] occurred in November, 1999 and were cited previously as item #14.}

The Narrative Summary contains this elaborative information/analysis:

[deleted]

{The baby born with congenital anomalies (US01-22842 @ AVE 009085) was cited previously as item #13. The case related to Cardiogenic Shock, Subacute Prosthetic Valve Thrombosis and Fetal Death [ZA01-00210] was cited previously as item #14.}

Two cases related to valvular thrombosis [ZA01-00209 and ZA01-00210] were noted to have prompted cessation of the study under which they had been treated ("High-Dose Lovenox vs. Standard Heparin/Coumadin," ENO-ZA-301, as per AVE 009109); Anti-Xa levels were reported in the latter case.] One adverse event reported during this year (3/29/1999 - 3/28/2000) was noted to have involved a fetus (AVE 009133). No action was taken relative to drug-labeling after this comprehensive study (AVE 009151).

Assessment: More information is needed related to the missing page #23, GB01-05569, and the omission of numerous case-discussions (summarized herein) from this précis.

AVE 009209 depicts a 35 year-old woman who had a fetus who had an intrauterine death; "the Danish Medicines Agency considers the Death Fetal as possibly related to Lovenox." No further information was provided regarding the circumstances thereof.

Assessment: It is absolutely mandatory that further information be provided regarding the circumstances surrounding this event; particularly noting the governmental comment, there must have been a probe initiated and, thus, further data must have been accrued.

AVE 009301 depicts a pregnant woman who had a fetus with a transiently absent heartbeat; she had a history of a positive anti-cardiolipin.

Assessment: More information is needed regarding this patient's course.

AVE 009307 depicts a woman who had a fetus with delayed growth.

Assessment: More information is needed regarding this patient's course.

AVE 009309 depicts a woman who had a fetus with delayed growth and Factor V Leiden.

Assessment: More information is needed regarding this patient's course.

AVE 009592 depicts a fetal death in a woman with two prior fetal deaths and two coagulopathies (positive anti-cardiolipin and Factor V Leiden).

Assessment: This case was felt by the neonatologist not to be Lovenox-related.

AVE 009594 depicts a fetal death in a woman with two coagulopathies (positive anti-cardiolipin and Factor V Leiden).

Assessment: This case was felt by the neonatologist not to be Lovenox-related.

Table 1: Serious and Unexpected Events

The Follow-Up column has abbreviations ["I" and "F-1"] which are not defined. Also, the numbering-system does not cross-reference specific cases; a cross-walk would, thus, need to be surmised (based on the case reviews). What is vital to appreciate, here, is the absence of any follow-up information when even the diagnosis of "fetal damage" exists.

Assessment: What is particularly remarkable both in this physician's distillation and the tabular presentation of the data is the absence of a consistent database. For example, pathologic assessment of the placenta is not consistently reported, and this is information that could have been acquired in "real time" when reports of adverse actions arrived. Even if other explanations for any given finding might be conjured—such as a conjoint "abruption placenta"—the inability to "reach" even this rudimentary level of analysis impugns the ability to claim that the public-protection role of the pharmaceutical house has been upheld. This is not a pass-through activity; rather, it is to be based on the best measured judgments regarding the need to maintain an academic/clinical level of inquiry that would not wish to miss any potentially-toxic drug-effect. That the public trust in the FDA is predicated on the maxim "*primum non nocere*" is central to its basic charge; although efficacy data are accrued and dutifully reported, toxicity data are emphasized. Further analysis of this entire data-set is segregated to a distinct site in this report, *infra*.

Table 2: Serious and Expected Events

Assessment: It is surprising that these findings were "expected" in contrast to the prior tabulation, when the diagnoses are essentially indistinguishable. Indeed, in the absence of any notation that there might have been a concomitant congenital anomaly to explain fetal-demise [again, recognizing the limited capacity to cross-reference the clinical data], why these data are also sparse (for example, again not having pushed for documentation of pathological examination of the placenta) raises credibility questions regarding the intensity of "intellectual curiosity" which should be magnified under these circumstances. Noting the discrepancy between the numbers of administered-dosages and case-reports, pursuit of but any one case carries the potential to affect the global marketplace.

Index, Table 4: SU Events by System Organ Class

Assessment: As noted *supra*, these groups appear almost arbitrary (and, if nothing else, carry tremendous capacity to overlap). All are better perceived as "syndromes" rather than "diagnoses," for each can be explained (in isolation) by either myriad or a unitary underlying pathogenesis. It is also noted that another category contrasts with this status; "Congenital and Familial/Genetic Disorders" are distinguished "with a difference" and, therefore, have not even been listed herein. Having adopted a self-limited approach to discerning what might have caused these findings clearly emerges as a pervasive concern.

Index, Table 5: SE, NE, & NU Events by System Organ Class

Assessment: Three items are in the "Pregnancy, Puerperium and Perinatal Conditions" section: Intrauterine Death (3 initial reports), Complications of Pregnancy NOS (2) and Feeding Problems in Newborn (1). None had generated follow-up reports, and there was again no effort to cross-walk the databases because the specific cases comprising each listing were not provided.

Why the higher number of such conditions in other tables was diminished was not explained; again, absent an analytic component, it was not possible to discern what fundamental criteria were employed when these tables were being compiled.

Events Resulting in Death

Assessment: Two listings are in the "Pregnancy, Puerperium and Perinatal Conditions" section: "Intrauterine Fetal Death" related to US01-25235; one with follow-up "I" (submitted 7/24/2000) and another with follow-up "F-1" (submitted 10/13/2000). Thus, as noted repeatedly, why cases were consistently deleted is unclear.

Listing of 15-day Alerts

Assessment: This listing of all cases that would be perceived as potentially relevant, again contains information that cannot be correlated with that depicted elsewhere.

Index of FDA 3500's

Assessment: Two tables are provided. The first is an index of cases, and the second is a compilation of the cases by body-system. The first includes US01-24659 (Fetal Death); follow-up reports were generated for only seven cases. The second includes one Fetal Disorder, which was then calculated (with whatever import) as 3.57% of all events in this body system, 0.5% of all events, one patient, 4% of patients in this body system, and 1.22% of all patients. [The "body system" was "body as whole."] Again, how it is discerned that there was only one "Fetal Death" is not rectified with other data-sources.

Narrative Summary

Assessment: This set of recommendations is definably deficient, for it states that only one case of placental hemorrhage and detachment had been discerned; multiple cases of placental hemorrhage had been reported, not withstanding the lack of due diligence when pursuing the need for follow-up information. The degree to which the stated hazard has been captured in marketing of this agent is to be addressed following the data-analysis.

AVE 010009 depicts a 30 year-old woman with Factor V Leiden (and Gilbert's Disease) who experienced a retroplacental hematoma (and, thus, fetal loss) @ 35 weeks'gestation. At laparotomy, the coagulopathy had worsened (with thrombocytopenia, azotemia and "hepatic cytolysis"), revealing "a large hemoperitoneum and perihepatic hematoma." Transfusions [pRBCs (17 units), FFP (17 units), salt-poor albumin (3) and platelets (3)] yielded improvement during the subsequent two days, but no follow-up report exists. "Lovenox was considered as a suspect drug with a doubtful imputability."

Assessment: *Au contraire*, there is no doubt that the spontaneous hemorrhage was caused by the Lovenox, probably triggering DIC via systemic release of products of conception. The Lovenox was both "suspect" and "imputable." [To be discussed *infra*, also, is the phenomenon of hemorrhage between the blood circulations of mother and fetus.]

AVE 010033 depicts an article about subchoroidal hemorrhage ascribed to Lovenox because "the acute onset of the bleeding with the close proximity to the beginning of Lovenox therapy makes our diagnosis the only probable diagnosis for this patient." The authors found one additional case-report of this association and surmised rationale.

Assessment: This is an example of hemorrhage associated with Lovenox in which the independent authors conclude a cause/effect relationship due both to knowledge of how the drug works and to awareness of tight chronologic contiguity. It is this level of basic "clinical suspicion" that would reasonably warrant reporting and further investigation. This is what these authors chose to do, and this is what Aventis is expected to do.

AVE 010038 depicts a newborn with initial distress; no further data were provided.

Assessment: This baby's experience also could have had a hemorrhagic component and, thus, inquiry regarding the particulars of what transpired should have been initiated.

AVE 010135 depicts a newborn who died from hemoperitoneum by rupture of hepatic capsule and placental lesions with multiple infarctions; the baby experienced bradycardia. The baby's mother had a history of anti-phospholipid syndrome.

Assessment: The placental infarctions can't be reflexly ascribed to the autoimmune state. Unlike many of the (unflagged, here) abortion-related cases (in which the placenta is not routinely examined) this case entailed a term-birth. Therefore, both in isolation and related to other cases, the placental pathology could be explained by use of Lovenox.

AVE 010161 depicts a woman who developed *abruptio placentae* and fetal demise.

Assessment: The report ends with this statement: "The physician assessed the causal relationship between events and treatment with Lovenox as 'not associated' but mentioned that a third party had expressed a suspicion of causal relationship between premature abruption of placenta and treatment with Lovenox." It would be desirable to know the identity of the initial physician—particularly if he/she is an Aventis employee—and the rationale for having reached this all-encompassing conclusion.

Distillation of Distillations

These 31 assessments focus on two broad categories of concern raised by this exhaustive review of the Aventis files related to Lovenox. The first is evidence of transplacental transmission of this drug, perhaps associated with an exaggerated fetal-maternal leak… and perhaps a distinct phenomenon; offering potential physiologic explanations is not the proper role of this medical expert. The second is evidence that there was no follow-up of additional reports of potential transplacental transmission of this drug, with particular note of the absence of a focus on the need to examine the placenta pathologically; again, conjuring alternative obstetrical explanations (*e.g.*, ascribing anything adverse to *abruptio placentae*, spontaneous abortion, or an occult congenital/developmental anomaly) is not the proper role of this medical expert, particularly when provided such paltry data.

Entire categories of information could not be analyzed, such as the dosage employed and whether any of the recognized monitoring tests were actually applied (either in a clinical or in a research setting). For example, **AVE008506** [cited at the bottom of page 116] mirrors the instant case. Assume *abruptio placentae* occurs in as many as 0.5% of all pregnancies, due not to anticoagulants but to idiopathic disruption of the decidual layer of the blood vessels. Might this be conjured as the total explanation for what transpired?

According to an Internet resource [http://www.emedicine.com/med/TOPIC6.HTM] which was updated on 1/11/2007, pathologic analysis of the placenta may prove decisive: "After delivery of the placenta, a retroplacental clot may be noted. Another possible finding involves extravasation of blood into the myometrium, which produces a purple discoloration of the uterine serosa. This phenomenon is known as a Couvelaire uterus."

Also, due to variable numbering systems and data summaries that appeared to omit cases, it was not always possible to assume that comparable case-presentations overlapped. That some cases were dismissed by anonymous physicians is also grist for probing, for the desire to engage in professional denial can blind investigators from unearthing facts. This would necessarily define why some findings were "expected" and why classification of symptoms/syndromes supplanted the need to distill precise findings/diagnoses.

Clearly, any pregnant woman who has been anticoagulated is intuitively at increased risk to develop obstetrical complications, due either to the underlying diagnosis/diagnoses that had prompted this medicinal intervention or to potential iatrogenic complications.

Therefore, it is anticipated that a obstetrical review will confirm both the concerns raised regarding prenatal care provided in the instant mother/daughter case [detailed *supra*] and the need for further data regarding how women were managed in the reported cases. Having detailed evidence for *in utero* drug exposure and injury, this physician defers to others with obstetrical expertise to define the relative import of this phenomenon when the overall issues of patient management are scrutinized. For example, "outlier" data (such as an isolated Apgar Score) might actually be challenged as incompatible with clinical information, but this can be accomplished only by a physician who can draw upon an experiential expertise that this physician obviously/admittedly totally lacks.

To be precise, one case [**AVE008506**] provides a model as to what should have warned Aventis of the potential for Lovenox to cross the placenta, not withstanding; indeed, perhaps this is the case that prompted the insertion of the "one case warning" in the PDR.

And in one instance [**AVE 008519**], neonatal thrombocytopenia suggested the potential for Lovenox to have previously crossed the placenta. In another instance [**AVE 008530**], neonatal hemorrhage (intrathoracic) again suggested transplacental drug transmission.

Another case [**AVE 010009**] revealed widespread hemorrhage that was antedated by a retroplacental hematoma, again suggesting that the primary event was caused by the transplacental transmission of this drug (indirectly leading to the death of the fetus).

And one final case [**AVE 010135**] revealed a fetus had died from hemoperitoneum, again suggesting that the primary event had been transplacental drug transmission.

These five cases are on-point, but nowhere in the Aventis filings are they aggregated. Further, many additional cases require a modicum of follow-up; they have not been tabulated here because of uncertainty regarding whether there is significant overlap. Others require clarification regarding the status of the placenta—as referenced *supra*—because it is necessary to deal in particular with the inclusion of at least one other state (*abruptio placentae*) within the differential diagnosis of subsequent fetal demise. And still others require investigation as to how Aventis did or did not choose to follow-up; adopting a passive role consistently through this process appears to have been a pattern.

Not to be inappropriately married to one's own particular statement expressing a sense of feeling aghast at what had been unearthed, re-restated is this reaction to the unfulfilled need for basic due diligence when a pharmaceutical house is engaged in self-scrutiny:

Assessment: What is particularly remarkable both in this physician's distillation and the tabular presentation of the data is the absence of a consistent database. For example, pathologic assessment of the placenta is not consistently reported, and this is information that could have been acquired in "real time" when reports of adverse actions arrived. Even if other explanations for any given finding might be conjured—such as a conjoint "abruption placenta"—the inability to "reach" even this rudimentary level of analysis impugns the ability to claim that the public-protection role of the pharmaceutical house has been upheld. This is not a pass-through activity; rather, it is to be based on the best measured judgments regarding the need to maintain an academic/clinical level of inquiry that would not wish to miss any potentially-toxic drug-effect. That the public trust in the FDA is predicated on the maxim "*primum non nocere*" is central to its basic charge; although efficacy data are accrued and dutifully reported, toxicity data are emphasized. Further analysis of this entire data-set is segregated to a distinct site in this report, *infra*.

Although this section appears to have been composed in conclusory language, it is felt that its contents—particularly those that have been underlined—flow inevitably from the database without insertion of editorialization. On the other hand, knowledge of the role of the FDA (and charge from the FDA to *inter alia* Aventis) was invoked as indicated.

Theorizing

Although it is not the goal of this effort to define the pathogenesis of what may occur when Lovenox is administered, information has been received regarding what might have transpired (in this and other cases). It is included herein so that a "working hypothesis" can be provided sufficient (at the very least) to articulate how Lovenox may exert a transplacental non-mutagenic effect (with or without concomitant thrombocytopenia):

> Maternal IgG are the only antibodies which traverse the placental barrier and can enter fetal circulation. The fetal/neonatal immune system is immature until the first several days following birth, so the only IgG source found in the newborn is from the mother. Fetal IgG provides protection against infection, an evolutionary advantage during gestation. However, excessive fetal IgG levels can bind to fetal platelet blood cells and be taken out of fetal circulation, thereby causing thrombocytopenia. The pro-/anti-coagulation balance (hemostasis) would then become imbalanced, provoking DIC-like fetal bleeding and clotting.
>
> Standard therapy for severe Neonatal Allo-Immune Thrombocytopenia ["NAIT"] including transfusions of IV-IG and platelets was carried out and found to be beneficial for Savannah, supporting the view that IgG had caused this phenomenon; over-abundance of infused IgG swamped the spleen's IgG receptors and stopped fetal clearance of platelet-IgG complexes from the fetal circulation, even as platelet infusions helped to build the platelet count back towards normal.
>
> Since the neonatal hematologist (Dr. Weil) acquired tests (*e.g.*, Wisconsin) to rule-out common etiologies of NAIT, it was concluded to be idiopathic. Yet, this would be consistent with a possible drug effect, particularly noting the positive indirect but negative direct Coombs test results; this is consistent with the hypothesis that free antibodies circulating in the blood serum were present maternally and transferred to the fetus.
>
> Lovenox may have caused a slow low-level immunoresponse maternally where IgG and other antibodies were building up but remained relatively "clinically" asymptomatic; note no blood tests were carried out to monitor such emerging conditions. HIT can occur and can be easily diagnosed and would have been symptomatic to the mother. However it remains to be determined (or found in tests performed by Aventis) if LMWH (low molecular weight heparin) is immunogenic to a lesser, subclincal manner. If so, the IgG component could have been transferred to the fetus while the mother remained asymptomatic. This would be an insidious drug effect for the fetus, which would have remained relatively asymptomatic as well.

Because of the lack of basic clinical data (as aforementioned), no opinion is offered here regarding whether this would be the sole way Lovenox could be toxic to the fetus.

Marketing and Promotion

There are a few facets of the activities pursued by Aventis that can be easily categorized. They have been direct and indirect; because the latter routinely uses the medical literature as a vehicle, conflict-of-interest information is needed for all submitted authorships. Focusing on Laboratory Testing and Warnings allows some of these data to be elucidated but, again, others having greater expertise in this arena may invoke these observations through analysis thereof employing methodologies of which this physician is unaware.

In 1993-1995 [*see* AVE 005369 from 13:1,A], an advertisement advised that, in patients with normal pre-surgical coagulation profiles, there is "*NO* required monitoring of coagulation times." As noted previously, there are many tests (such as anti-Xa) which had been raised as potential monitoring studies, and there are virtually no data regarding their use in any high-risk population (such as pregnant women). Therefore, apparently, Aventis did not consider whether any such testing (through protocol studies, for example) might be indicated, if for no other reason than to identify patients who might have an erratic response to the drug (and, thus, then trigger more monitoring of its activity, thereby yielding the potential that an altered dosage would diminish potential toxicity).

Another recommendation is somewhat ambiguous, albeit interpretable on its surface: "The use of Lovenox is not recommended in patients with artificial (prosthetic) heart valves, including pregnant women." This advice [*see* AVE 005615 from 13:1,I] could be viewed as including pregnant women among those in whom its use is not recommended; otherwise, why single-out them (as opposed to other patients with risk-factors)? Yet, probably, the sentence was written because of some of the case-reports reviewed *supra*. It probably need not include the last three words, for they add nothing whatsoever to the import of the recommendation; their presence, contrariwise, suggests a broader sweep.

In any case, during March, 2002 [*see* AVE 013940 from 13:1,H], Aventis sent a letter to Health Professionals announcing revision of the Warnings, including the following:

> *Non-teratogenic Effects*: There have been post-marketing reports of fetal death when pregnant women received Lovenox Injection. Causality for these cases has not been determined. Pregnant women receiving anti-coagulants, including enoxaparin, are at increased risk for bleeding. Hemorrhage can occur at any site and may lead to death of mother and/or fetus. Pregnant women receiving enoxaparin should be carefully monitored. Pregnant women and women of child-bearing potential should be apprised of the potential hazard to the fetus and the mother if enoxaparin is administered during pregnancy.

Noting that Aventis had consistently advised against the need to perform monitoring labs, its advice that "pregnant women receiving enoxaparin should be carefully monitored" cries for elaboration for, as a stand-along sentence, it is absolutely meaningless…even were it actually to be perceived as a "disclaimer." [How should this monitoring occur? Which test is advised? How often should it be acquired? Would dosage be affected?]

Although a publication issued in 2007 obviously would not have affected what doctors did or didn't know a half-decade prior, noting the information provides insight as to the contents of what might have been issued years previously. Thus, if the information here is based on old data, it should have been captured in old documents (which it wasn't). Consider [*see* AVE 014113 from 15:3,C]:

5.9 Laboratory Tests

Periodic complete blood counts, including platelet count, and stool occult blood tests are recommended during the course of treatment with Lovenox. When administered at recommended prophylaxis doses, routine coagulation tests such as Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT) are relatively insensitive measures of Lovenox activity and, therefore, unsuitable for monitoring. Anti-Factor Xa may be used to monitor the anticoagulant effect of Lovenox in patients with significant renal impairment. If during Lovenox therapy abnormal coagulation parameters or bleeding should occur, anti-Factor Xa levels may be used to monitor the anticoagulant effects of Lovenox [see *Clinical Pharmacology (12.3)*].

Fetal Risk Summary

Lovenox is not predicted to increase the risk of developmental abnormalities. Lovenox does not cross the placenta, based on human and animal studies, and shows no evidence of teratogenic effects or fetotoxicity.

Clinical Considerations

It is not known if either dose adjustment or monitoring of anti-Xa activity of enoxaparin are necessary during pregnancy.

Pregnancy alone confers an increased risk for thromboembolism that is even higher for women with thromboembolic disease and certain high risk pregnancy conditions. While not adequately studied, pregnant women with mechanical prosthetic heart valves may be at even higher risk for thrombosis [see *Warnings and Precautions (5.7) and Use in Specific Populations (8.6)*]. Pregnant women with thromboembolic disease, including those with mechanical prosthetic heart valves and those with inherited or acquired thrombophilias, have an increased risk of other maternal complications and fetal loss regardless of the type of anticoagulant used.

All patients receiving anticoagulants such as enoxaparin, including pregnant women, are at risk for bleeding. Pregnant women receiving enoxaparin should be carefully monitored for evidence of bleeding or excessive anticoagulation. Consideration for use of a shorter acting anticoagulant should be specifically addressed as delivery approaches [see *Boxed Warning*]. Hemorrhage can occur at any site and may lead to death of mother and/or fetus. Pregnant women should be apprised of the potential hazard to the fetus and the mother if enoxaparin is administered during pregnancy.

Data

•*Human Data* - There are no adequate and well-controlled studies in pregnant women. A retrospective study reviewed the records of 604 women who used enoxaparin during pregnancy. A total of 624 pregnancies resulted in 693 live births. There were 72 hemorrhagic events (11 serious) in 63 women. There were 14 cases of neonatal hemorrhage. Major congenital anomalies in live births occurred at rates (2.5%) similar to background rates.

There have been postmarketing reports of fetal death when pregnant women received Lovenox. Causality for these cases has not been determined. Insufficient data, the underlying disease, and the possibility of inadequate anticoagulation complicate the evaluation of these cases.

Omitted from the marketing materials [contained in multiple binders] promoting DVT prophylaxis within hospitals is citation of any of the Warnings regarding pregnancy.

Also, it is recognized that there are other types of low-molecular-weight-heparins, to wit:

*LOVENOX Therapeutic Class defined as a market basket consisting of:
Lovenox® (enoxaparin sodium) Injection
Fragmin® (dalteparin sodium) – a registered trademark of Pharmacia Corporation
Normiflo® (ardeparin sodium) – a registered trademark of American Home Products
Orgaran® (danaparoid sodium) – a registered trademark of N.V. Organon Corporation
Innohep® (tinzaparin sodium) – a registered trademark of Leo Pharmaceutical Products Ltd.
Arixtra® (fondaparinux sodium) – a registered trademark of Sanofi-Synthelabo Inc.

No effort has been made to review/compare/contrast the literature generated by study of these other agents; the focus herein has remained trained upon Lovenox (of Aventis).

Finally, noted but not addressed are myriad data related to marketing, managed care cost, pharmaceutical partnering and other business-level activities; again, the focus is clinical.

Of-interest is a 6/15/2002 article from *OB/GYN News* that summarized the posture that was most favorable to Aventis; the most absolute level of reassurance was as follows:

But according to Dr. Charles Lockwood, the revised label should not prevent physicians from using the drug in most pregnant women. "There is no reason to change practice in any way except to avoid low molecular weight heparin in women with mechanical prosthetic heart valves," said Dr. Lockwood, professor and chair of obstetrics and gynecology at New York University, New York.

"The agent does not cross the placenta, providing no biological plausibility for such a risk. Secondly, a large study by Dr. J. Lepercq and associates [BJOG 108(11):1134-40, 2001] described pregnancy outcomes in 604 women treated with enoxaparin and observed a congenital anomaly rate of only 2.5%. And lastly, the variety of anomalies reported by Aventis and their rare occurrence strongly suggests no specific malformation pattern or increased frequency," he said.

To summarize, this Expert Report has traced the key-facts in this case through a series of analytic "hoops" that can be accessed expeditiously by noting the "(first page)" of each of the concepts discussed: Standing (1), Database (3), Assertions (6), Narrative (6), Medical Malpractice Issue Components (16), Baby Savannah Short-Term Sequellae (16), Baby Savannah Long-Term Sequellae (32), Depositions (32), Aventis-written PPI (35), Recapitulation of Medical Malpractice Issue Components (37), Cocaine (37), Periventricular Leukomalacia (38), Alternative Anticoagulants (40), Theory of the Case Against Aventis (42), Monitoring (42), Current PPI (72), Aventis Toxicity Files (75), Cross-Reference of Files and Internal Analysis Pages (81), Distillation (116), Distillation of Distillation (124), Theorizing (126), and Marketing and Promotion (127).

These analytic points must now be cross-walked with the allegations in the complaint [as per the (undated) Amended Motion for Judgment, #34462, ¶ 36)]:

36. Aventis was negligent in the following particulars:

a. Aventis is promoting this drug for use in pregnancy despite the fact that there are no adequate and well-controlled studies of safety in pregnant women;

b. Aventis has failed to provide adequate warnings of the risks of using Lovenox during pregnancy, even though there have been post marketing reports of fetal deaths when pregnant women received Lovenox injections.

c. Aventis has been negligent in the design, testing, manufacture and marketing of Lovenox;

d. Aventis has been negligent in that they have provided a package insert that is confusing and contradictory;

e. Aventis has been negligent is leading doctors to believe that no testing is necessary to monitor pregnant women who are receiving Lovenox; and

f. Aventis has not provided adequate information to doctors prescribing Lovenox to pregnant women for them to know how or when to prescribe Lovenox and to know how to monitor the safety of Lovenox during pregnancy.

Regarding each of these specific assertions, the following conclusions have been drawn regarding the conduct of Aventis with regard to the use of Lovenox in pregnant women:

a. It is promoted absent adequate and well-controlled safety studies.

b. There are no adequate warnings as to its risk, despite the existence of post-marketing reports of fetal deaths.

c. There has been negligence in its design, testing, manufacture and marketing.

d. The patient package insert is confusing and contradictory.

e. Doctors have been led to believe that monitoring tests are not needed.

f. Doctors have not been educated regarding the indications for and monitoring of its use.

These points are illustrated in the following fashion. There is no doubt that it has been promoted as being safe in pregnant women; indeed, the most current recommendations only exclude those with artificial heart valves. There have been no safety studies thereof. The warnings do not capture the essence of the information provided via case-reports, even those that are marginally complete when depicting fetal deaths; even if only one was related to another diagnosis (*abruptio placentae*), there was an obligation to convey the existence of any such "differential diagnosis" to the practitioner, thereby arming him/her with necessary information that would then be included within the Informed Consent process when dealing with the patient. Negligence in the acquisition, follow-up and analysis of post-marketing case reports necessarily affects adversely the methodology employed when designing and implementing its promotion, when advising which tests might be best employed when monitoring its use, when manufacturing an optimal agent for anticoagulation in this high-risk patient group, and when promoting its use therein. The evolving patient-package-insert ["PPI"] does not capture the necessary information, and certain sections are either/both confusing/contradictory when (for example) advising that pregnant women be "monitored." Physicians have been constantly reassured that this agent is immediately effective and need not be monitored, despite the existence of available tests that could—particularly in a high-risk population—ameliorate toxicity. Overall, physicians have not been informed as to its proper use and monitoring in the high-risk population of pregnant women, with particular regard to the need to decrease the risk of neonatal hemorrhage (not withstanding potential obstetrical delays).

One final observation is highly germane: the specific pathological changes associated with *abruptio placentae* [*see* page 124] were not noted in the instant case [*see* page 9].

If any further information is needed (such as a more extensive review of the more recent toxicity reports), please do not hesitate to contact me.

Sincerely,